A TEST OF AN INTERVENTION TO PROMOTE PAP TESTING IN A GROUP OF WOMEN LIVING WITH HIV

By

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ABSTRACT

Background: Cervical cancer is the second most common type of cancer among women worldwide. Women with human immunodeficiency virus (HIV) bear a disproportionate burden of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN), that result from persistent high-risk Human Papillomavirus (HPV) infection. HIV clinical practice guidelines recommend two Pap tests in the year following diagnosis, and if both are normal, yearly thereafter. Nationally, only 25% of women meet this recommendation. The mean annual Pap testing rate for federally-funded HIV centers is only 55.7%. In 2009, quality improvement statistics from the Johns Hopkins Hospital Adult HIV Clinic, a large urban HIV center, revealed an annual Pap testing rate of 59%. This occurred despite interventions to address adherence issues were implemented, including nurse case management, co-location of HIV and gynecology services, flexible scheduling, and continuity of care. Women keep their appointments for HIV primary care more often than for gynecology care in the adult HIV Clinic, so an intervention that takes place during a primary care visit could improve cervical cancer screening rates. The availability of HPV testing provides a unique opportunity to increase perceived susceptibility to and severity of cervical cancer among women with HIV, and to encourage follow-up Pap testing. Detection of high-risk strains of the virus indicates a higher risk for high grade CIN and cancer, while a negative HPV test predicts a less than 2% risk of developing CIN. Women can perform HPV testing easily through vaginal self-collection in a primary care visit. Studies of women without HIV who do not have regular Pap testing have demonstrated that self-collected HPV testing and results counseling increases the overall screening rate, and women who test positive for HPV have a high rate of follow-up Pap testing. Self-collected HPV testing and results counseling could be utilized in the HIV primary care setting to promote Pap testing among

women with HIV.

Objectives: This dissertation study was a randomized trial to test whether receiving self-collected HPV testing and results counseling in HIV primary care would increase completion of Pap testing in a group of women a hospital-based outpatient Adult Clinic for HIV Care. The study was informed by the Health Belief Model (HBM), which posits that screening behavior will increase if persons at risk for disease have a cue to action that increases their perception of susceptibility to and severity of the disease. In this study, the HPV test and results counseling were cues to action that also correctly identify women at increased for disease.

Sampling, design and methods: To achieve these aims, 97 women who were late for Pap testing were recruited for participation while they were at an HIV care appointment. They were randomized to HPV self-collection and results counseling, or to a control group receiving usual care. Six months after enrollment, medical records were reviewed for completion of Pap testing in the intervening months.

Findings: Self-collected HPV testing and results counseling did not improve Pap test attendance when compared with usual care as experienced by the control group. Overall, 35% of the entire sample completed their Pap tests within 6 months of the baseline visit. Perceived threat of cervical cancer did not change for the intervention group, even when the HPV test was positive. The follow-up interview rate for the Perceived Threat scale was 91%.

Conclusions: Self-collection of cervico-vaginal cells for HPV testing was feasible in this population. Overall the study served as an effective intervention to promote Pap testing. High follow up rates overall demonstrated that intensive interventions to improve cervical cancer screening are effective.

Advisor: Hayley Mark, PhD, RN

DEDICATION

This dissertation study is dedicated to my children:

Sonia and Bridget Murphy Anger, and

Daniel and Katya Anger.

Thank you for your love and for believing in me.

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CHAPTER ONE: INTRODUCTION

SIGNIFICANCE

Cervical cancer is the second most common type of cancer among women worldwide. (1) Women with human immunodeficiency virus (HIV) bear a disproportionate burden of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN), that result from persistent high-risk Human Papillomavirus (HPV) infection. (2-5) Women with HIV experience high rates - often over 50% - of HPV infection because of their weakened immune systems, (6) so annual Pap testing is critical to prevent cervical cancer. (7) However, many women with HIV do not engage in recommended Pap testing, resulting in increased risk for high grade CIN and cancer (8-10) and high treatment costs. (11) Thus convenient, effective interventions that promote engagement in care are needed to increase annual Pap testing in this group that experiences a disparity in health. (12) HIV clinical practice guidelines recommend two Pap tests in the year following diagnosis, and if both are normal, yearly thereafter. (7) Nationally, only 25% of women meet this recommendation. (8) The mean annual Pap testing rate for federally-funded HIV centers is only 55.7%. (13) In 2009, quality improvement statistics from the Johns Hopkins Hospital Adult HIV Clinic, a large urban HIV center, revealed an annual Pap testing rate of 59%. This occurred despite interventions to address adherence issues were implemented, including nurse case-management, co-location of HIV and gynecology services, flexible scheduling, and continuity of care. Women keep their appointments for HIV primary care more often than for gynecology care in the HIV Clinic, so an intervention that takes place during a primary care visit could improve cervical cancer screening rates. (14)

Interventions that increase individuals' perception of susceptibility to and severity of disease have successfully increased screening behaviors. (15-18) The availability of HPV testing

provides a unique opportunity to increase perceived susceptibility to and severity of cervical cancer among women with HIV, and to encourage follow-up Pap testing. HPV testing involves analyzing a sample of cervicovaginal cells for the presence of high-risk HPV strains. Detection of high-risk strains of the virus indicates an increased risk for high grade CIN and cancer, (19) while a negative HPV test predicts a less than 2% risk of developing CIN. (20-25) HPV testing can be easily conducted by women themselves through self-collection (26-30) in a primary care visit. (31) Studies of women without HIV who do not have regular Pap testing have demonstrated that self-collected HPV testing and results counseling increases the overall screening rate, and women who test positive for HPV have a high rate of follow-up Pap testing. (32-35) Thus self-collected HPV testing and results counseling could be utilized in the HIV primary care setting to promote Pap testing among women with HIV.

This study was a randomized trial to test whether receiving self-collected HPV testing and results counseling in HIV primary care will increase completion of Pap testing in a group of women attending the Johns Hopkins Hospital Clinic for Adult HIV Care. The study was informed by the Health Belief Model (HBM), which posits that screening behavior will increase if persons at risk for disease have a cue to action that increases their perception of susceptibility to and severity of the disease. (15) Here, the HPV test and results counseling were cues to action that also correctly identified those women at higher risk for disease.

SPECIFIC AIMS

Among women living with HIV who attend the Johns Hopkins Hospital Clinic for Adult HIV Care, and who are 18 months or more from their last Pap test:

1. Test whether an intervention using self-collected HPV testing and results counseling will increase the proportion of Pap test completion by six months for women who test positive for HPV compared to women who test negative for HPV, and to women in the control group.

Hypothesis 1.1: A higher proportion of women who test positive for HPV will complete Pap testing by 6 months, compared to women who test negative for HPV.

Hypothesis 1.2*:* A higher proportion of women who test positive for HPV will complete Pap testing by 6 months, compared to women in the control group.

Hypothesis 1.3: The intervention group will have higher odds of Pap test completion than the control group, controlling for possible confounders such as HIV viral load, education, age, and history of substance abuse.

2. Determine if self-collected HPV testing and results counseling increases perceived susceptibility to and perceived severity of cervical cancer for women who test positive for HPV compared to women who test negative for HPV, and to women in the control group.

Hypothesis 2.1: The mean change score for the Perceived Susceptibility to and Perceived Severity subscales of the Champion Health Belief Model scale (modified for cervical cancer) will be higher for women who test positive for HPV than for women who test negative for HPV.

Hypothesis 2.2: The mean change score for the Perceived Susceptibility to and Perceived Severity subscales of the Champion Health Belief Model scale (modified for cervical cancer) will be higher for women who test positive for HPV than for women in the control group.

To achieve these aims, 94 women who were late for Pap testing were recruited for participation while they were at an HIV care appointment. They were randomized to HPV self-collection and results counseling, or to a control group. Six months after enrollment, medical records were reviewed for completion of Pap testing in the intervening months.

REVIEW OF LITERATURE

For women living with human immunodeficiency virus (HIV), cervical cancer (CC) is an acquired immunodeficiency syndrome (AIDS)-defining illness. Over 50% of women with HIV also have HPV infection. Because of persistent high-risk HPV infection, rates of invasive CC are 4-5 times higher for women with HIV than for other women. (35) Despite this heightened risk, many women with HIV do not have recommended Pap testing. Importantly, women with HIV who do receive CC screening and follow-up have rates of CC that do not exceed that of HIV negative women. (36)

Women with HIV report numerous reasons for missing annual Pap testing, including disliking the examination, embarrassment, fear of pain or discomfort, (37) lack of knowledge about risk, (38) and lack of access to services. (39) Other studies show that women who do not have regular screening experience the Pap test as negative, do not understand its significance (40) or do not like having a male provider. (41) Many interventions succeed by improving access to care. (42) While it is essential to continue improving access to care, it is also important to utilize other innovative interventions to encourage high-risk women to engage in cervical cancer screening and gynecologic care.

HPV self-collection and results counseling is a unique intervention that allows women to become more involved in their own care, while at the same time providing them with information about the cause of cervical cancer, plus an extremely accurate risk assessment without the need for a pelvic exam. HPV DNA testing has been used in cervical cancer screening since 2004 and is within the standard of care for screening women over age 30. (43) Its optimal use for women with HIV is unclear at this time. (7) HPV testing is sensitive for cervical disease even when samples are collected vaginally, with good agreement between self-collected and

clinician-collected HPV tests, (44-49) so many researchers have studied HPV vaginal self-collection strategies. (49-57) Studies of vaginal self-collection for HPV testing show high sensitivity for histology-confirmed high-grade CIN lesions, (50-67) and high levels of participation among women offered self-collection in a primary care setting. (31) Therefore, a self-collected high-risk HPV test offered by clinicians in an HIV primary care setting is feasible and would provide high-risk women with an accurate message of their own risk for cervical cancer.

In this study, the Health Belief Model (HBM)'s constructs of perceived susceptibility and perceived severity, which can be combined into the concept of perceived threat, are helpful in understanding the mechanism by which self-collected HPV test and results counseling could help increase women's adherence to Pap testing. In other areas of cancer screening, HBM-based interventions utilizing risk counseling to increase patients' perceptions of risk for breast cancer have improved mammography adherence, specifically among African-American women. (15,68) Risk counseling with personalized risk assessments was also shown to increase short-term adherence to colorectal cancer screening. (69) A recent randomized trial demonstrated that education focused on HPV testing and follow-up significantly increased Pap test follow up for women with a history of abnormal Pap tests. (18) Large European studies of women who did not respond to invitations for cervical cancer screening programs showed that offering HPV self-collection and results increased screening participation rates overall, and women who tested positive for HPV followed up with Pap testing at very high rates, 80-95%. (32-34) Qualitative research has demonstrated that women with HIV reported that motivation to follow up after an abnormal Pap test was related to understanding their increased risk for cervical cancer, personal relationships with clinical staff, and being directly involved in their own care. (70)

BACKGROUND AND SIGNIFICANCE

This study is important because it focuses on women who are at increased for cervical disease, but are not participating in annual cervical cancer screening. Women with HIV in the Johns Hopkins Adult HIV Clinic who did not receive Pap testing in the preceding 18 months were identified. Among these women, a randomized trial was conducted to test whether self-collected HPV DNA testing and subsequent results counseling would lead to improved Pap testing. The study is significant because it rigorously tested a unique intervention that provided accurate risk information for high-risk patients. It also tested the health behavior constructs underlying the intervention by measuring perceived susceptibility and severity at two time points.

DISSERTATION ORGANIZATION

This dissertation is organized into five chapters. The first chapter provides an overview of the study, with attention to the purpose and specific aims of the dissertation and a review of the relevant literature.

Chapter Two (manuscript one) describes cervical cancer screening in the current context of HPV testing and vaccination. There is additional literature reviewed on women with HIV and their risk for cervical cancer, and the sensitivity and specificity of self-collected HPV testing.

Chapter Three (manuscript two) describes the main outcome of the study, the relationship between HPV testing and follow-up Pap testing. This randomized controlled study tested whether offering self-collected HPV tests and results counseling to a group of women living with HIV would improve Pap testing rates within 6 months of the baseline visit.

Chapter Four (manuscript three) is an analysis of Perceived Threat scores on the Champion Health Belief Model scale among women both at baseline and at follow-up. The analysis focused on the HPV self-collection group.

Chapter Five presents a summary of the dissertation and an exploration of its findings, with a discussion of relevance and importance, and how the findings will inform future research in this area.

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CHAPTER TWO: MANUSCRIPT ONE: Murphy, J. and Mark, H.: Cervical Cancer Screening in the Era of Human Papillomavirus Testing and Vaccination. *J Midwifery Womens Health* 2012;00:1–8. doi: 10.1111/j.1542-2011.2012.00207

ABSTRACT

Cervical cancer screening algorithms have changed with the introduction of testing for human papillomavirus (HPV) and better understanding of the natural history of HPV. This review was undertaken to present recent developments related to cervical cancer screening, with HPV testing as a focus. Specifically, guidelines now recommend initiating cervical cancer screening at age 21, stopping at age 65 to 70 if previous tests are normal, and screening no more than every 2 to 3 years. Human papillomavirus testing is now incorporated into guidelines for cervical cancer screening in the United States, with the major impact being the lengthening of recommended screening intervals. Primary screening with HPV testing, although not yet approved in the United States, may serve to increase access to care for the millions of underserved women worldwide who bear most of the burden of cervical cancer. Despite clear guidelines from authoritative sources, many clinicians (including midwives) overscreen women. In cervical cancer screening, as in many areas of women's health care, performing tests that are unlikely to result in useful information may lead to harm.

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and the world (1) and is a necessary cause of cervical cancer. The two main risk factors for cervical dysplasia and invasive cervical cancer are persistent oncogenic HPV infection and lack of access to screening. (2) With the advent of HPV vaccination of women aged 9 to 26 years in 2006, and widespread availability of HPV testing, cervical cancer screening will change

radically in the years to come. Certified nurse-midwives/certified midwives (CNMs/CMs) play a critical role in preventing cervical cancer and in educating women on HPV infection and vaccination. Thus, it is important that they remain up-to-date on current findings related to practice and disease prevention.

This article is a review of the recent (within 5 years) scientific literature on cervical cancer epidemiology, screening strategies, and US guidelines, with an emphasis on the use of HPV testing in screening for cervical cancer. We also review guidelines for cervical cancer screening in special populations (i.e., adolescents, older women, and women living with HIV), underserved women (both in the United States and internationally), and women's and clinician's responses to rapidly changing recommendations. Finally, we discuss the newest technologies and strategies in the continuing fight against cervical cancer.

METHODS

This integrative literature review was performed using the key words "human papillomavirus," "cervical cancer," "guidelines," and "Pap testing" to search MEDLINE, CINAHL, and Google Scholar. Hand searching through references of selected articles was also performed to ensure completeness.

RESULTS OF REVIEW

Cervical Cancer Epidemiology

Worldwide, the cervical cancer burden falls most heavily on women in developing countries. In the United States, screening and referral for treatment of cervical dysplasia, relying on exfoliative cytology for primary screening, have helped to decrease the incidence of invasive cervical cancer. (3) In this article, Papanicolaou testing refers to cervical cancer testing using exfoliated cervical cells, whether it is using smears on conventional glass slides or liquid-based

cytology, where cervical cells are suspended in preservative solution and slides created thereafter. Recent data from 2008 compiled by the International Agency for Research on Cancer show that in North America cervical cancer is now ranked 13th of cancers affecting women, although fourth among those affecting women aged 15 through 44 years, with an age-standardized incidence rate of 5.7 new cases of cervical cancer occurring each year per 100,000 women. This incidence rate ratio is similar to that of Northern Europe (8.3/100,000) and Australia/New Zealand

(5.0/100,000). (4)

Papanicolaou testing has generally been met with widespread acceptance in the United States and has greatly reduced incidence and mortality related to cervical cancer. (5,6) However, African American and Hispanic women are still disproportionately impacted. Hispanic women have the highest incidence rate of cervical cancer (11.5/100,000), followed by African American women (10.2/100,000). African American women have the highest cervical cancer mortality of US racial and ethnic groups at 4.3/100,000, twice the cervical cancer mortality of white women. The geographic distribution of cervical cancer clusters shows increased rates of invasive cervical cancer among pockets of women with poor access to screening, in underserved urban areas, (6) and in the rural South. (2)

In contrast, outside of the developed world where Papanicolaou testing is readily available, cervical cancer is the second or third most common women's cancer in all but the northernmost regions of Africa. The age-standardized incidence rate ratio in southern Africa ranges from 26.8 to 34.5 per 100,000 women and in southern Asia ranges from 15.8 - 24.5 per 100,000. The starkest disparity between the developed and developing worlds is seen in the difference in

cervical cancer mortality; in 2008, of the 274,967 women who died from cervical cancer in the world, 88% (241,818) were in the developing world. (4)

Risk Factors for Cervical Cancer

Human Papillomavirus

Recent changes in cervical cancer screening guidelines rely on current understanding of the natural history of oncogenic HPV and its role in development of cervical cancer. There are more than 100 strains of HPV, 13 of which are considered oncogenic. In particular, the presence of HPV 16 or 18 is associated with a higher risk of developing high-grade cervical precancer. (7) Human papillomavirus infection is extremely common. In the most recent National Health and Nutrition Examination Survey, overall HPV prevalence in the United States was 26.8% among women aged 14 to 59 years. Human papillomavirus prevalence increased each year from14 to 24 years and then gradually declined through age 59. Human papillomavirus 16 and 18 were detected in 3.4% of the

participants. (8) Other earlier studies suggest higher HPV prevalence, such as 43% among college-age women. (9)

The development of cervical cancer is a decades-long process, and details about immune response, clearance, and latency of HPV infection are unclear at this time.10 Transient infection with oncogenic HPV is common, but persistent infection with high-risk forms of HPV, which is necessary for development of cervical dysplasia and cancer, is less so. Persistent infection usually refers to detection of virus for more than 6 months. (7,11,12) Some women may experience high-risk HPV persistence with no development of cervical dysplasia, (13) and classic studies showed that more than 90% of high-risk HPV infections clear within 2 years with no intervention. (14,15) However, for the approximately 5% of HPV infections that do not clear

for more than 2 years, there is a greater than 40% risk of developing high-grade cervical precancer lesions. (10)

Other Risk Factors for Cervical Cancer

The American Cancer Society (ACS) identifies risk factors for the development of cervical cancer that may contribute to altering a woman's immune response and lessening her ability to clear high-risk HPV.16 The risk factors include smoking, combined oral contraceptive use, early or multiple pregnancies, Chlamydia trachomatis infection, poverty, family history of cervical cancer, and diet. Among these, recent studies

confirm a strong association between smoking and HPV-related cervical disease. (17–20) Although earlier reports of associations between combined oral contraceptive use and increased risk for HPV infection were criticized for failing to account for sexual activity and condom use, some recent studies that controlled for these factors still show higher risk for persistent HPV infection among users. (20,21) Centers for Disease

Control and Prevention (CDC) guidelines for combined oral contraceptive use, which are based on those of the World Health Organization, note the increased cervical cancer risk but conclude that the benefits outweigh the risks. (22)

The American College of Obstetricians and Gynecologists guidelines from 2009 also identify higher risk for cervical dysplasia and cancer among women with HIV or other immunosuppression or who were exposed to diethylstilbestrol in utero or who have been treated previously for cervical dysplasia. (23) Recent immigrants from countries with no cervical cancer screening program are also at higher risk. (24)

Primary Prevention: Human Papillomavirus Vaccines

Two vaccines for HPV have been approved for women in the last 5 years. A quadrivalent vaccine (Gardasil) was approved in 2006 and confers immunity against 2 oncogenic strains of HPV (16 and 18), which together account for 70% of cervical cancers, and 2 strains (HPV 6 and 8) that together cause 90% of genital warts. The quadrivalent vaccine is also known as HPV4. The bivalent vaccine (Cervarix) became available in 2009 and protects against acquisition of HPV 16 and 18 but does not prevent genital warts. Both vaccines have been shown to have similar clinical effectiveness, and the bivalent vaccine is less expensive. Clinical trials found that these vaccines were greater than 98% and 93% effective, respectively, against HPV 16 and 18. (25,26) The quadrivalent vaccine has recently been approved for use in young males for prevention of genital warts and anal cancers, (27) with an observed efficacy of 60.2%. (28) The longevity of the immune protection and whether a booster vaccine is needed are not yet known. Both vaccines appear to be safe and well tolerated.

Current recommendations are similar for women and men aged 9 to 26 years. The quadrivalent vaccine is given as a 3-injection series, with the second and third injections administered 2 and 6 months after the first. The newer bivalent vaccine is approved for women and girls aged 9 to 25 years and has the same dosing schedule.28 Uptake rates for both HPV vaccines have been low among women in the United States.

The National Health Interview Survey found that among girls aged 11 to 17 years, only 28.9% had received at least one dose in 2010. (29) Uptake rates are much higher in England, where data from 2010 indicated that of girls aged 12 to 13 years that were offered the bivalent vaccine, 82% received one dose, and 66% received 2 doses.30 This difference is likely in part due to the fact that vaccines are delivered in school in England rather than only through primary care providers and are fully covered by the national health plan in England. (31) In the United States, some

insurance companies do not cover HPV vaccination, although the Vaccines for Children program covers it for women aged 9 to 18 years who are Medicaid-eligible, have no insurance, or who are members of American Indian or Alaska Native communities. (32) In 2009, only 29 state Medicaid programs covered the vaccine for women aged 21 to 26 years. (33)

Eventually, the effectiveness of screening with cytology-based methods may change with widespread population immunity to HPV 16/18 and reduction in the number of abnormal lesions. (34) The vaccines do not protect against HPV infection that is already present, nor do they protect against all types of oncogenic HPV strains, thus screening for cervical cancer is still recommended. (27)

Secondary Prevention: Human Papillomavirus Testing and Cervical Cancer Screening

Testing for HPV in general clinical practice became possible approximately 10 years ago with US Food and Drug Administration (FDA) approval of technology to test for HPV DNA and to distinguish between low-risk and high-risk strains of the virus. The first such test approved for clinical use in the United States was the Digene HC2 HPV DNA test (Qiagen, Germantown,Maryland). There are FDA-approved HPV tests from other manufacturers, including the Cobas HPV test (Roche, Basel, Switzerland) and Cervista HPV (Hologic, Bedford, Massachusetts). These tests detect 13 high-risk, or oncogenic, strains and produce a qualitative (positive or negative) result for high-risk HPV. Cobas and Cervista HPV tests can also be used to identify the presence of HPV 16 or 18. When added to Papanicolaou screening, high-risk HPV testing improves Papanicolaou screening sensitivity. (35) This is important because despite the success of the US screening program in driving down cervical cancer incidence, recent studies have demonstrated troubling low sensitivity for Papanicolaou testing and thus missed precancerous cervical lesions. (36)

There are 3 sets of cervical cancer screening guidelines from national clinical practice organizations. The American College of Obstetricians and Gynecologists released its guidelines in 2009 (23) and an additional guideline for adolescents in 2010. (37) In March 2012, both the United States Preventive Services Task Force (USPSTF) (38) and a combined working group of the ACS, American Society for Colposcopy and
Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP)39 released guidelines. The guidelines all recommend screening with Papanicolaou tests utilizing either conventional slides or liquid-based cytology and vary their recommendations for HPV testing and frequency of Papanicolaou testing depending on the age of the woman.

Significantly, there is no longer any guideline that recommends annual Papanicolaou testing for low-risk women. All call for cervical cancer screening to begin at age 21. (37–39) For women aged 21 to 29 years, American College of Obstetricians and Gynecologists guidelines23 recommend cytology-only screening every 2 years, while USPSTF (38) and ACS/ASCCP/ASCP (39) guidelines recommend cytology-only screening every 3 years. For women aged 30 to 65 years, American College of Obstetricians and Gynecologists guidelines (23) recommend screening with cytology every 2 to 3 years for women with 3 negative annual cytology tests. United States
Preventive Services TaskForce guidelines recommend screening with cytology every 3 years or cytology and HPV contesting every 5 years. (38) The ACS/ASCCP/ASCP guidelines recommend a preferred strategy of cytology and HPV co-testing every 5 years, with cytology-only screening every 3 years as an acceptable alternative. (39) Human papillomavirus vaccination does not change any cervical cancer screening recommendations. Both American College of Obstetricians and Gynecologists (23)

and ACS/ASCCP/ASCP (39) guidelines review use of HPV testing for triage of abnormal Papanicolaou test results. For women aged under 30 years, the qualitative HPV test can be used to triage Papanicolaou tests with mildly abnormal results (i.e., atypical squamous cells of undetermined significance or ASCUS). If a woman receives such a Papanicolaou test result, an HPV test can be performed either in a separate visit or, if she had a liquid-based test initially, on remaining cytology fluid. If the HPV test result is positive, the patient should be referred for colposcopy. For women aged over 30 years, if the Papanicolaou test result is normal, and the HPV test result is positive, they should be referred for colposcopy. The guidelines also discuss performing HPV genotyping for the most virulent HPV strains, HPV 16 and 18. If a woman has a negative Papanicolaou test result but tests positive for either HPV 16 or 18, she should be referred for colposcopy. Abnormal Papanicolaou test results of any grade above ASCUS warrant colposcopy,

regardless of HPV results.

Table 1 lists current recommendations from the expert panels. The ASCCP published practice guidelines in 2006 addressing management of abnormal cervical cancer screening test results. These guidelines do not address general screening issues but provide guidance about abnormal Papanicolaou test result triage and screening certain populations of women, (40) and are therefore not included in the table.

Table 1. Recommendations for Cervical Cancer Screening

Population	American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology,[a] 2012	United States Preventive Services Task Force,[b] 2012	American College of Obstetricians and Gynecologists, 2009[c]; under 21, 2010[d]
Age <21 y	Do not screen	Do not screen	Do not screen
Age 21-29 y	Screen with cytology[e] every 3 y. HPV co-testing not recommended	Screen with cytology[e] every 3 y	Screen with cytology[e] every 2 y for women aged 21-29 y
Age 30-65 y	Screen with cytology[e] and high-risk HPV co-testing every 5 y (preferred) or with cytology[e] every 3 y (acceptable)	Screen with cytology[e] every 3 y or with cytology[e] and high-risk HPV co-testing every 5 y	Screen with cytology[3] every 3 y for women with 3 negative cytology[3] tests. HPV co-testing is appropriate
Age >65 y	No screening if negative prior screens	No screening if adequate prior screening and no risk factors	Stop screening between ages 65-70 y with 3 consecutive cytology[e] and no abnormal cytology[e] within 10 y
After hysterectomy	No screening if prior screening showed no high-grade cervical dysplasia or cancer	No screening if hysterectomy was performed for benign disease	No screening if hysterectomy was performed for benign disease
Received HPV vaccination	No change in screening recommendation	No change in screening recommendation	No change in screening recommendation

[a]Source: Saslow et al.[38]
[b]Source: United States Preventive Services Task Force.[39]
[c]Source: American College of Obstetricians and Gynecologists, 2009.[23]
[d]Source: American College of Obstetricians and Gynecologists, 2010.[37]
[e]Papanicolaou test or liquid-based cytology.

Special Populations: Adolescents, Older or Pregnant Women, and Women with HIV

If adolescent women have Papanicolaou testing against recommendations, they are considered poor candidates for triage of ASCUS Papanicolaou test results with HPV testing because they are likely to show HPV infection that usually regresses without treatment. Repeat Papanicolaou testing in one year is recommended, with referral to colposcopy for repeated abnormal cytology or for high-grade squamous intraepithelial lesions. (37) Little has changed in current recommendations for pregnant women and older women. However, the 2009 American College of Obstetricians and Gynecologists guidelines clarify that it is not necessary for women with low-grade squamous intraepithelial lesion Papanicolaou test results to have colposcopy during pregnancy and recommend colposcopy after 6 weeks postpartum. (23) All 3 guidelines recommend that screening can be discontinued in later life (after age 65) when previous screening has been normal. (23,38,39)

Because of the increased risk for cervical cancer in women living with HIV, clinical practice guidelines recommend 2 Papanicolaou tests in the year after diagnosis and if both are normal, yearly thereafter. (41) Once women with HIV are infected with HPV, they do not clear the infection effectively, especially when their CD4 counts are low. (42) While highly active antiretroviral therapy (HAART) has greatly improved the overall health status of persons with HIV, there is uncertainty regarding the effect of HAART on cervical dysplasia and invasive cervical cancer. Some studies show a decrease of cervical intraepithelial neoplasia and invasive cervical cancer with widespread use of HAART starting in 1996, (43) but others do not. (44) Other studies demonstrate conflicting findings about the effects of HAART on clearance of HPV lesions. Overall, women living with HIV are more likely to experience persistent oncogenic HPV infection, which promotes cancerous progression of cervical lesions.45 Immunosuppression, as evidenced by low CD4 count (<200) and high viral load, is strongly associated with development of invasive cervical cancer. (46,47) Despite these observations, there is ample evidence that women with HIV who have optimal gynecologic follow-up care can avoid cervical cancer. (48) According to ASCCP, immunosuppressed women with ASCUS lesions can be triaged with HPV testing in the same way that other women are managed, (40) while the Centers for Disease Control and Prevention and American College of Obstetricians and Gynecologists recognize no role for HPV testing for women with HIV. (41,49)

Responses to HPV Testing and Changing Guidelines: Women and Clinicians

Women's knowledge of HPV and its etiologic role in cervical cancer has changed since introduction of the first HPV vaccine in 2006.50 Early studies showed poor levels of knowledge about HPV and even less accurate knowledge about cervical cancer. (51) More recent studies demonstrate widespread accurate knowledge about HPV (52) even among women who have not

yet received the vaccine. (53) There are subgroups of women who have less accurate knowledge of HPV, such as Latina women and those with more conservative religious views about sex, some of whom believe that induced abortion causes cervical cancer. (54)

Researchers have expressed concern about possible adverse psychosocial effects of widespread use of HPV testing, because a positive HPV test result labels women as having a sexually transmitted infection. (55) Studies show that the knowledge that HPV causes cervical cancer can cause shock and concern. (56) Women who test positive for HPV may feel increased shame and stigma, (57) screening-related distress, (58) or decreased sexual satisfaction. (59) However, "normalizing" HPV infection by emphasizing its commonness was effective in reducing anxiety and feelings of stigma and shame among women who tested positive for HPV. (60) Another study showed a significant decrease in women's concerns about testing positive for HPV after an HPV educational intervention. (61)

Questions have arisen about whether women are willing to accept less frequent cervical cancer screening, given the known success of this test in reducing cancer mortality and its connection to the annual gynecologic examination. While some women are reluctant to change their own cervical cancer screening behaviors, the majority of women would follow extended screening intervals, and older women would stop, if their clinicians recommend it. (61−63) Clinicians have been slow to change cervical screening practices. Despite release of guidelines over the past decade that recommend less frequent screening (ACS in 2002, American College of Obstetricians and Gynecologists in 2002 and 2009, USPSTF in 2003), many clinicians demonstrate practice patterns inconsistent with these guidelines. (64) Adherence to guidelines varies by geographic location and specialty, with CNMs and obstetrician-gynecologists most likely to adhere to practice guidelines when compared with other specialties. (65) However, most

provider groups, including midwives, (66) consistently overscreen by initiating screening too early, screening too frequently, and not stopping screening for older women.

Improving Care in the Developed World: New Technology

In the developed world, HPV testing has allowed more accurate identification of women at risk for cervical dysplasia and cancer. Polymerase chain reaction technique (67) has allowed genotyping of the dozens of HPV strains but was not used clinically until 2009 when the FDA approved genotype testing for triage of negative Papanicolaou with positive HPV test results, allowing identification of the more virulent HPV 16/18

strains for immediate colposcopy referral instead of waiting to repeat the tests in one year per the usual guidelines.(68) Other biomarkers may be used in the future to improve cervical cancer screening, such as detection of specific proteins produced by HPV-infected cervical cancer cells, E6 and E7 oncoproteins. (69) Eventually, it may be possible to use specific tests for these oncoproteins, which use swab or brush collection technology, in self-sampling strategies for large-scale population

screening. (70)

Improving Care for Underserved Women: Moving Screening from the Clinic to Home

High cervical cancer incidence in the developing world is largely due to large numbers of unscreened women.(71) Procedures such as visual inspection with acetic acid that allow screening and treatment at the same visit have shown efficacy in detecting cervical cancer and reducing cervical cancer deaths. (72) However, a recent large randomized trial in India showed the superiority of a one-time HPV test followed by treatment in reducing mortality from cervical cancer, when compared to visual inspection with acetic acid. (73)

High-risk HPV testing has the potential to increase screening rates among underserved women because the technology can be used for primary screening in the home rather than in clinics. Self-collection of samples is a relatively simple intervention that could increase cervical cancer screening for hard-to-reach women. This is common in gynecology (e.g., urine testing for Chlamydia trachomatis and Neisseria gonorrhea) (74) and shows high levels of acceptability among women. (75) Self-collected HPV tests could allow for more complete screening for cervical cancer in the population; women could mail swabs to a laboratory from home (76) or cervical cancer screening could be combined with primary care visits or home visits, as in a recent study in the Mississippi Delta region. (77) Self-collected HPV tests are performed using tampons, small Dacron swabs, or soft cytobrushes. Women insert the collection device vaginally, follow instructions for the particular device (for example, the cytobrush is inserted vaginally and rotated 3 times), and place the device in a collection container with preservative. The collection devices are mailed to a laboratory for processing. Studies comparing accuracy of HPV results between self-collected and clinician-collected HPV samples found good agreement between them. (78) In addition, rapid point-of-care tests for HPV and antigen markers of HPV-infected cervical cells show promise in allowing rapid, accurate testing for HPV and immediate referral for treatment. (79)

DISCUSSION

Dramatic changes in cervical cancer screening guidelines in recent years reflect the availability of HPV tests, evolving knowledge about the causal relationship between HPV and cervical cancer, the efficacy of screening, and the potential harms of overscreening. In March 2012, the USPTF, ACS, ASCCP, and ASCP updated the guidelines for cervical cancer screening, with an unequivocal recommendation of screening no more than every 3 years. In the future, screening

for cervical cancer prevention will continue to evolve secondary to HPV vaccination uptake and increasing availability and acceptability of HPV testing as a primary screening tool. New technologies such as HPV DNA testing, whether used in home or clinic-based testing or as part of cytology screening, may ultimately be effective in improving outcomes.

For women's health clinicians, it is essential to continue to engage women in discussion about the risk factors for cervical cancer and to encourage vaccination for those who are eligible. It is also important to follow national guidelines for cervical cancer screening which, if utilized appropriately, can safely lengthen screening intervals for women who are at low risk for cervical cancer. Overscreening and then overtreatment of transient HPV-related cervical dysplasia is painful, expensive, and burdensome to women and can increase risk for hemorrhage, infection, and preterm birth. (80) Researchers have questioned the need for other aspects of generally accepted gynecologic care, such as the annual pelvic examination, given that noninvasive testing is now available via self-collection strategies for common sexually transmitted infections and that the bimanual examination yields little clinical information in asymptomatic women. (81) Midwives thus may need to reconsider the purpose of the well-woman visit and re-envision it as a primary care health promotion encounter.

As HPV vaccination and molecular testing for HPV continue to change the face of surveillance of HPV, cervical dysplasia and cervical cancer, more research is needed about clinicians' and women's perceptions of changing cervical screening intervals. Finally, there are continuing important policy implications in making funding available for a new kind of annual well-woman examination as well as population-based HPV vaccination of young women and men, appropriate cervical cancer screening, and treatment of precancerous lesions.

The midwifery philosophy of care includes the beliefs that every person has the right to "equitable, ethical, accessible quality health care that promotes healing and health," and moreover, "complete and accurate information to make informed health decisions." (82) We have an obligation to women we care for to provide, whether in childbearing or in gynecology, care that is safe, evidence-based, and appropriate to their needs. Understanding the rationale for current guidelines for cervical cancer screening will help us to better meet these needs.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose

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ADDITIONAL LITERATURE REVIEW

Additional literature review: What follows is a review of literature not included in the manuscript, but important to the dissertation proposal: Prevalence of HPV and cervical cancer among women living with HIV, and sensitivity of self-collected samples for HPV testing.

C. Prevalence of HPV and cervical cancer among women with HIV: For women living with human immunodeficiency virus (HIV), cervical cancer (CC) is an acquired immunodeficiency syndrome (AIDS)-defining illness. (1) HPV, the cause of cervical cancer, (2) is common among sexually active adults, with over 40% prevalence among young women in the United States. (3) Over 50% of women with HIV also have HPV infection. (4) Once women with HIV are infected with HPV, they do not clear the infection effectively, especially when immunocompromised. (5) Women with HIV experience higher rates of oncogenic HPV infection and persistent HPV infection than women without HIV, (4,6) which are strong predictors of cancerous progression of cervical lesions. (7)

Therefore, rates of invasive CC are 4-5 times higher for women with HIV than for other women. (8) In particular, severe HIV-related immunosuppression, as evidenced by low (<200) CD4 count and high viral load, is associated with development of invasive CC. (5)

With the advent of highly active antiretroviral therapy (HAART) in 1996, the prevalence of many AIDS-defining illnesses decreased. This is an area of debate with conflicting results. Briefly, in the case of high grade cervical lesions (HSIL) and invasive cervical cancer, some cohort studies have shown decreased prevalence with HAART,[9,10,11] and another study demonstrated HAART's efficacy in increasing clearance of HPV, although regression of extant abnormal lesions did not occur. (12) However, a systematic review by Bratcher and Sahasrabudde (2010) reviewing nine extant studies of HAART's effects on HPV incidence,

persistence and clearance showed mixed results. (13) Adherence to HAART may prove to be a major factor in successful suppression of HPV. A 2010 study from the WIHS group examining the relationship of cervical cancer risk and HAART adherence showed that excellent adherence to anti-HIV medication was associated with clearance of HPV, with a significant reduction in HPV prevalence (OR 0.60, 95% CI 0.44-0.81) and more rapid clearance of HPV (HR 2.35, 95% CI 1.01-5.18) but not with incidence or clearance of oncogenic HPV-related squamous intraepithelial lesions (incidence OR 1.56 95% CI 0.47–5.21, clearance OR 2.20 95% CI 0.62–7.73) (14) Another 2010 study exploring the effects of HAART initiation on HPV incidence in adolescents with HIV showed no effects, though the short follow up period of 13 months may not have allowed enough time after HAART initiation to show a result. (15) A study of 2325 South African women with HIV demonstrated that higher CD4 count was associated with decreased odds of high grade lesions after adjustment for demographic factors (OR 0.82, 95% CI 0.77-0.87 per increment of 100 CD4 cells/μ L). An analysis of repeated Pap smears over a year in a subgroup of 1153 women demonstrated significant associations between level of CD4 and HAART status, and progression of cervical precancerous lesions from normal or low grade to high grade. CD4 level and HAART were not associated with regression of lesions in this group. (16) Another study from Canada demonstrated significant regression of cervical intraepithelial lesions in 456 women on HAART (HR, 3.32; P = .02). (17) In a 2013 study of menopause and HIV, HAART use was associated with half the risk of progression of SIL (HR 0.47, 95% CI 0.33–0.68, p = 0.0001) (18).

There is strong evidence that women living with HIV who engage in long-term regular cervical cancer screening and follow-up care can avoid ICC, as demonstrated in the WIHS cohort study. Women in this study are followed closely, with cervical cancer screening at regular

intervals. There was no statistically significant difference in ICC between HIV-negative (incidence rate 0 / 100,000 person-years) and –positive women (21.4 / 100,000 person-years) after over 10 years of follow-up (p= 0.59). (18) Because of the effectiveness of regular cervical cancer screening in preventing ICC in women with HIV, clinical practice guidelines continue to recommend regular, annual Pap testing (19), and given that ICC is rare in appropriately screened women with stable HIV disease, it may be possible to begin to use HPV testing to improve screening. (20)

D. Sensitivity of self-collected samples for HPV testing: Studies of performance of self-collected HPV vary in materials and methods. Qiagen's Hybrid Capture II (hc2) is readily available for use in a clinical setting at Johns Hopkins Hospital, so this proposal will focus on studies related to performance of this HPV test. One type of analysis compared performance of HPV self-collection, clinician-collection, and liquid-based Pap testing in their ability to predict HSIL on cervical biopsy. This is best for evaluating self-collected hc2 HPV testing use in a clinical population, since the desired outcome is superior detection of actual cervical disease. An early study reported HPV self-collection's sensitivity was 86.2% (95%CI 74.6-93.9%) as compared to HPV clinician-collection's sensitivity 98.3% (95% CI 90.8-100%), while sensitivity for Pap testing was 77.6% (No CI was reported). (21) Two later studies reported high sensitivity of self-collected samples; one at 96.3% (22) and another at 100%, with excellent agreement with clinician-collected samples. (23) Two other studies reported lower sensitivity of HPV self-collected samples and HPV clinician-collected samples – 66.1% vs. 83.9% (24) and 71.3% vs. 95% (25) respectively; these represented statistically significant differences, although both HPV collection methods had superior sensitivity when compared with Pap testing. Another reported 83% sensitivity of HPV self-collection, vs. 77% for Pap testing and 95% for samples collected

by a clinician. (26) Belinson et al (2012) demonstrated significantly lower sensitivity for self-collected samples using the Cervista™ qualitative HR-HPV system (70.9% (62.7–78.3) as compared to clinician-collected 95.0% (90.0–98.0), but this difference disappeared when using a more sensitive PCR system, with both self- and clinician-collected samples having sensitivity of 94.3% (89.1–97.5). (27)

Table 1: Sensitivity/Specificity of Self-Collected HPV: Studies with Dacron swab and HC2

Study	**N**	**HPV self-collection**	**HPV clinician-collection**	**Pap test**	**Endpoint**
Sellors et al 2000[21]	200	Sensitivity: 86.2%(95%CI 74.6-93.9) Specificity: 53.5%(95%CI 45-61.9)	Sensitivity: 98.3%(95% CI 90.8-100) Specificity: 52.1%(95%CI 43-60.6)	Sensitivity: 77.6% Specificity: 81% (No CIs reported)	HSIL
Wright et al 2000[24]	1415	Sensitivity: 66.1%(95% CI 52.1-77.8) False positive rate: 17.1% (95% CI, 15.1-19.3)	Sensitivity: 83.9%(95% CI 71.2-91.9) False positive rate: 15.5% (95% CI, 13.6-17.7)	Sensitivity: 60.7%(95% CI 46.7-73.2) False positive rate: 12.3% (95% CI, 10.5-14.2)	HSIL for HPV collection; compared with Pap endpoint of LSIL or higher
Chang et al 2002[22]	1194	Sensitivity: 96.3% Specificity: 91.8% (95% CI not reported)	Sensitivity & specificity: Not reported but "no significant difference" with self-collected	Sensitivity: 79.2% Specificity: 93.4% (95% CI not reported)	
Belinson et al 2003[26]	2047	Sensitivity: 83% Specificity: 86% (95% CI not reported)	Sensitivity: 95% Specificity: 85%(95% CI not reported)	Sensitivity: 77% Specificity: 98% (95% CI not reported)	HSIL
Salmeron et al 2003[25]	7868	Sensitivity: 71.3%(95% CI 61.3-79.6) Specificity: 89.2%(95% CI 88.5-89.9)	Sensitivity: 93.1%(95% CI 85.8-96.9) Specificity: 91.8(95% CI: 91.2-92.4)	Sensitivity: 59.4%(95% CI: 49.2-68.9 Specificity: 98.3%(95% CI: 98.0-98.6)	HSIL or higher
Dannecker et al 2004[23]	435	Sensitivity: 100% Specificity: 71.4% (95% CI NR)	Sensitivity & Specificity: NR but good agreement (κ=.71)	Not reported	Any CIN
Belinson et al 2012 [27]	10,000	Sensitivity: 70.9%%(95% CI 62.7–78.3) Specificity: 86.1(85.3–86.8) with	Sensitivity: 95.0 (90.0–98.0) Specificity: 90.3 (89.6–90.9) with qualitative	Not reported	CIN 3 or higher

		qualitative HPV test Specificity 94.3% (89.1–97.5) 87.5 (86.8–88.2) with PCR	HPV test Specificity: 94.3 (89.1–97.5)/ 89.4 (88.7–90.0) with PCR		

Other studies, listed below, compared agreement or concordance between HPV tests performed by women to those collected by clinicians during a pelvic exam. These three meta-analyses (28-30) pooled and analyzed concordance of self- and clinician-collected HPV tests. Ogilvie et al (28) used the clinician-collected sample as the gold standard, and found that concordance was 0.74-0.81 between the self- and clinician-collected samples. Petignat et al. found even higher concordance of 0.87, with a kappa statistic of 0.66. (29) The latest metaanalysis by Arbyn (2014) showed consistently lower sensitivity and specificity for self-collected versus clinician-collected samples when qualitative (positive or negative) HC2 or Cervista tests were used, though still the self-collected samples were more sensitive than Pap tests. This is in contract to PCR-based HPV tests which showed similar sensitivity and specificity when comparing clinician- and self-collected samples. (30)

Table 2: Meta-analyses of studies testing sensitivity/specificity and concordance between self-collected and clinician-collected HPV samples.

Study	Test	Sensitivity of self-collection	Gold standard	Agreement
Ogilvie et al 2005[26]	HC2 and/or PCR	0.74 (0.81 for referral clinics)	Clinician collected HPV test	NR
Petignat et al 2007[27]	HC2 and/or PCR	NR	Any positive test (collected by self or by clinician) was the reference standard	For HR-HPV, 87%; overall agreement between sampling strategies: Detection of HR-HPV kappa=0.66 (95%CI, 0.50 to 0.82)
Arbyn et al 2014 [28]	HC2, Cervista, PCR, other methods	0.85 for HC2 0.85 (0.81–0.90)	varied	0.88 when compared with clinician-collected

NR=not reported

Overall, although clinician-collected HPV samples are more sensitive, self-collected samples show better performance in detecting HSIL than Pap testing, and are close to the sensitivity of clinician-collected samples. These studies demonstrate that self-collected samples for HPV testing are sensitive for detecting HSIL, and could reasonably be offered to women who are not responding to attempts to perform clinician-collected cervical cancer screening.

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CHAPTER THREE: MANUSCRIPT TWO:

Title: SELF-COLLECTED HPV TESTING AND RESULTS COUNSELING AS AN INTERVENTION TO IMPROVE PAP TESTING AMONG WOMEN WITH HIV: A RANDOMIZED CONTROLLED TRIAL

Target journal: *Journal of Lower Genital Tract Disease*

ABSTRACT

Introduction

Convenient, effective interventions that promote engagement in gynecologic care are needed to increase annual Pap testing in women living with HIV, who experience a disparity in cervical cancer related to their HIV status. Self-collected HPV testing and results counseling could be utilized as an intervention to increase Pap testing among this group.

Methods

This was a randomized controlled trial of self-collected HPV testing and results counseling. Eligible participants were women over age 18, with HIV infection, attending an adult HIV Clinic for a primary HIV care visit, and whose last Pap test occurred 18 months or more from the baseline visit date. The primary outcome measure was completion of a Pap test at Johns Hopkins Hospital 6 months or less from the baseline study visit.

Results

A total of 94 women were enrolled in the study. There were no differences in Pap test completion when comparing HPV positive to HPV negative women, nor when comparing HPV positive to control group women. Overall, the Pap test completion rate for women in the study was over 35%.

Discussion

Self-collected HPV testing and results counseling did not improve Pap test attendance when compared with the control group. Self-collection of cervico-vaginal cells for HPV testing was feasible in this population. High follow up rates overall demonstrated that the study itself served to increase the overall Pap testing rate within 6 months for the study group.

INTRODUCTION

Cervical cancer is the second most common type of cancer among women worldwide. (1) Women with human immunodeficiency virus (HIV) bear a disproportionate burden of cervical cancer and its precursor, cervical intraepithelial neoplasia (CIN), that result from persistent high-risk Human Papillomavirus (HPV) infection. (2-5) Invasive cervical cancer (ICC) is an acquired immunodeficiency syndrome (AIDS)-defining illness. (6) HPV is common among sexually active adults, with over 40% prevalence among young women in the United States and even higher rates among women with HIV. (7,8) Once women with HIV are infected with HPV, they do not clear the infection effectively, especially when immunocompromised. (9) Women with HIV experience higher rates of oncogenic HPV infection and persistent HPV infection than women without HIV (9,10), which are strong predictors of cancerous progression of cervical lesions, causing rates of ICC that are 4-5 times higher for women with HIV than for other women. (11,12) In particular, severe HIV-related immunosuppression, as evidenced by low (<200) CD4 count and high viral load, is associated with development of ICC. (9)

Despite their heightened risk for cervical cancer, many women with HIV do not engage in recommended Pap testing. HIV clinical practice guidelines recommend two Pap tests in the year following diagnosis, and if both are normal, yearly thereafter. (13) Nationally, only 25% of HIV infected women meet this recommendation. (14) The median annual Pap test completion rate for federally funded HIV centers is 55.7%. (15) In the literature, women with HIV reported missing annual Pap testing due to disliking the examination, embarrassment, fear of pain or discomfort (16), lack of knowledge about risk (17), and lack of access to services. (18) In other studies, women who did not have regular screening report experiencing the Pap test as negative, did not understand its significance (19) their own increased risk, (20) and did not like having a

male provider perform the examination. (21) Women also have reported fears about Pap testing and pain associated with the examination. (16, 20)

Convenient, effective interventions that promote engagement in gynecologic care are needed to increase annual Pap testing in this group that experiences a disparity in health. (22) In the HIV Clinic, interventions to address adherence, including nurse case-management, co-location of HIV and gynecology services, flexible scheduling, and continuity of care were implemented. There is no scientific literature on co-location of services or the impact of nurse case-management on Pap testing for women with HIV. A recent study showed that women kept their appointments for HIV primary care more often than for gynecology care in the HIV Clinic, (16) so a cervical cancer screening intervention that takes place during an HIV primary care visit could prove feasible and increase improve cervical cancer screening rates.

Interventions that increase individuals' perception of threat from disease, operationalized as perceived susceptibility to and severity of disease resulting in perceived threat, have successfully increased screening behaviors like colonoscopy and mammography. (23-26) There is no study of perceived threat from HPV or cervical cancer among women with HIV. The availability of HPV testing provides a unique opportunity to increase screening for cervical cancer by increasing women's perceptions of personal threat from cervical cancer among women with HIV, and encouraging follow-up Pap testing. HPV testing involves analyzing a sample of cervicovaginal cells for the presence of high-risk HPV strains. Detection of high-risk strains of the virus indicates a increased for developing high grade CIN and cancer, (27) while a negative HPV test predicts a less than 2% risk of developing CIN. (27-31) HPV testing can be easily conducted by women themselves through self-collection (32-37) during a primary care clinic visit, (38) just as they may self-collect vaginal swabs for routine gonorrhea and chlamydia testing as suggested in

the 2010 CDC Sexually Transmitted Disease treatment guidelines. (39) Studies of women without HIV who did not have regular Pap testing demonstrated that self-collected HPV testing and results counseling increased the overall cervical cancer screening rate, and women who tested positive for HPV have a high rate of follow-up Pap testing. (40-43) Self-collected HPV testing and results counseling could be utilized in the HIV primary care setting to promote Pap testing among women with HIV.

The study was a randomized controlled trial to test whether receiving self-collected HPV testing and results counseling in HIV primary care would increase completion of Pap testing in a group of women attending an adult HIV Clinic for HIV care at a large urban hospital in the Mid-Atlantic region of the U.S. The study was informed by the Health Belief Model (HBM), which posits that screening behavior will increase if persons at risk for disease have a cue to action that increases their perception of threat from a disease. Perceived threat in the HBM is operationalized as perceived susceptibility to and severity of a disease. (23) In this study, the HPV test and results counseling were cues to action that also identified women at higher risk for disease. All HPV testing used was for high-risk, oncogenic HPV types. The purpose of the study was to examine whether an intervention using self-collected HPV testing and results counseling would increase the proportion of Pap test completion by six months, comparing women who test positive for HPV compared to women who test negative for HPV, and to women who receive control. Women living with HIV who attended the Johns Hopkins Hospital Adult HIV Clinic, and who were 18 months or more from their last Pap test were eligible for the study.

METHODS

Study Design and Sample

A randomized controlled trial was conducted at the Johns Hopkins Hospital Adult HIV Clinic for HIV Care in Baltimore, MD. This clinic provides HIV specialty care to approximately 3500 adults over 25 years of age. In 2009, approximately 900 of Adult HIV Clinic patients were women. Clinic staff estimated that 80% of women served by the clinic were African-American, with an average age of 45 (Jeanne Keruly, personal communication, 4/15/2011). The study was approved by the Johns Hopkins institutional review board.

Eligible participants were women over age 18, with HIV infection, attending the Adult HIV Clinic for a primary HIV care visit, whose last Pap test occurred 18 months or more from the baseline visit date, and who met the other inclusion criteria listed in Table 1.

INSERT TABLE 1 HERE

Study procedures

The Electronic Patient Records (EPR) of patients were searched to identify eligible women with HIV primary care appointments. On each day that an eligible woman had an appointment, the staff caring for the woman on that day were approached and requested that they give the woman written information about the study, which contained contact information for the researcher. Clinicians were aware of study inclusion criteria, and were encouraged to refer all eligible women for Pap testing. Once a woman contacted the researcher, she was asked if she wished to participate in a study about cervical cancer screening using a self-collected vaginal sample for HPV. Women agreeing to participate signed a consent form reviewing HPV's significance and the importance of annual Pap testing for women with HIV. The consent also gave access to medical and clinic records for review for study variables, as well as consent to study specimen collection. The researcher ensured that participants had access to a telephone, and obtained multiple contact numbers. Participants were interviewed about demographic

characteristics, and then answered questions from the perceived threat subscale of the Champion Health Belief Model scale, which was modified to reflect cervical cancer and screening for it. The Champion HBM Scale was designed to measure HBM-related constructs in relation to breast cancer. (44) Recent studies used a modified scale to measure the same constructs in relation to cervical cancer and Pap testing by replacing breast cancer and mammography with cervical cancer and Pap testing in test items. (45,46) Items are rated on a 5-point Likert-type scale (from 1 = strongly disagree to 5 = strongly agree), and responses within the scale were summed. Responses were coded such that a lower score indicate higher Perceived Susceptibility to and Perceived Severity of cervical cancer. In a 2011 study using the modified Champion HBM scale, the perceived susceptibility and severity scales each had a Cronbach's alpha level of 0.78, with test/retest reliability of 0.84 and 0.85 respectively. (46) In this study, test-retest reliability was 0.9675. Cronbach's alpha for the pre-baseline was 0.7802, and for post-baseline 0.6962. Women were given a $15.00 gift card for completing the baseline visit.

Participants were then randomly assigned into the intervention or control group. Using an HPV prevalence estimate of 50% among women with HIV, we allocated participants to the Intervention group and the Control group in a 2:1 ratio respectively. (8) For allocation of the participants, a computer-generated random list of assignments to the control or intervention group was used.

Intervention

There was no attempt to blind the intervention. Women in the intervention group were encouraged by their providers to make appointments for Pap testing. As part of study procedures, they were given a test kit for Qiagen Hybrid Capture II (hc2) high-risk HPV DNA test that includes a soft cytobrush. They were also given an instruction sheet detailing the use of the

cytobrush to self-collect cervicovaginal cells, which the researcher reviewed with them. Women went to a nearby washroom and performed the self-collection, and returned to the researcher with the sealed specimen, following institutional protocols for biohazard safety and specimen labeling. Afterwards, women were encouraged to make their appointments for Pap testing. HPV test results counseling was given by telephone at about two weeks after the baseline visit. Three to five weeks after the baseline visit, and after the HPV results call, women were called again and were interviewed to complete the perceived threat subscale of the modified Champion Health Belief Model scale.

Women in the control group were encouraged by their provider during their primary care appointment to make an appointment for Pap testing. This is usual care for this clinic. A brief Pap test reminder phone call was performed at two weeks after the baseline visit as an attention control, and in addition the perceived threat subscale of the modified Champion Health Belief Model scale was administered. To encourage retention for administration of the scale, both groups were offered an additional $20 gift card to complete a follow-up phone call for the modified Champion HBM scale perceived threat subscale by interview at 3-5 weeks.

Sample size

Sample size for the study was calculated using 80% power to detect an increase of 30% in the proportion of women completing Pap testing, comparing women who test positive for HPV to those in the control group, using a one-sided, two-group test for the difference in proportions and an estimated 80% Pap follow-up rate for women testing positive for HPV as reported in HPV self-collection studies. (40-43) Using these parameters we estimated that a total of 72 women should be enrolled, 24 in the control group and 48 in the intervention group. Additional women

were recruited to account for possible attrition, and a total of 94 women were enrolled in the study.

Statistical methods

Summary statistics included calculation of means and standard deviations for continuous variables, and numbers and percentages for categorical variables. Differences between group means were tested using one-way analysis of variance (ANOVA) if the data were normally distributed, and the Kruskal Wallis test if the outcome variable was not normally distributed. Differences between groups on categorical variables were tested using one-way ANOVA. Differences between groups on dichotomous variables were tested using Chi square. The main outcome measure of completion of Pap testing by 6 months after the baseline visit was tested using a one-sided, two-group test of proportions set at an alpha level of 0.05.

A total of 347 women's charts were assessed for eligibility prior to their clinic visit. Of those, 104 women came to their appointments and approached the researcher for screening. Seven women did not participate; 6 refused (6/104, or 5.7%), and 1 was ineligible. Ninety-seven women were enrolled in the study and randomized. After completion of study activities, 3 more women were excluded from analysis because medical records review revealed that they were ineligible for the study because their Pap tests were completed within 18 months of the baseline visit. The 3 women included one in the control group, one in the HPV positive group, and one in the HPV negative group. See the CONSORT Flow Chart (47) in Figure 1 below:

INSERT FIGURE 1 HERE

Thirty-one women were randomized to the control group, and 63 were randomized to the HPV self-collection group. Table 2 describes demographic characteristics of the entire study group, and then by subgroups. Of those 63 women, 27 tested positive for HPV for an HPV positive rate

of 42.9%. The control, HPV positive and HPV negative groups of women were similar in age, race, CD4 count, CD4 nadir, viral load control, history of substance abuse, household income, and type of insurance. There was a statistically significant difference in history of abnormal Pap among control and HPV positive women in a smaller subset of women (n=71) for whom there was a previous abnormal Pap test result in the chart. Women testing negative for HPV had a lower proportion of previous abnormal Pap test results than women in the control or HPV positive groups.

RESULTS

With regard to the main effect of the intervention, we compared groups in the proportion of Pap test completion within six months of the baseline visit. There was no statistically significant difference in Pap test completion between the control group (n=31) and the intervention group (N= 63). There was also no statistically significant difference in Pap test completion within 6 months between the HPV negative group (30.5%), and the HPV positive group (37.0%) (2 group test of proportions, p=0.30), nor between the HPV positive group (37%) and control group (38.7%) (2 group test of proportions, p = 0.55). Considering the entire sample, 35.1% (95%CI 55-74%) of the group completed Pap testing by 6 months.

Insert Table 2

All of the demographic and other factors listed in table 3 below were tested in bivariate logistic regression models to see if they predicted the final outcome of Pap test completion. None of the factors showed statistically significant relationships with the main outcome, so multiple logistic regression analysis was not performed.

Insert Table 3

In a secondary analysis of a subgroup of women with documented previous Pap test results, the HPV positive group had a statistically significantly higher proportion of women with a history of previous abnormal Pap test. Because this may be linked to HPV positivity, the subgroup of 71 women with previous Pap results was tested for independent effects on the final outcome using bivariate logistic regression analysis, and this showed no effects on the final Pap test outcome (p=0.482).

A small group of 9 women received incentives from their health insurance companies, like gift cards or cash, to complete Pap testing. Three of the women completed Pap testing, and six did not. There was no significant difference in Pap test outcome by receiving an additional non-study incentive (OR 0.92, 95% CI 2.2 – 3.9, p = 0.91).

DISCUSSION

Given the higher risk of cervical cancer among women with HIV and the low rates of adherence to Pap smear recommendations, it is clear that interventions to improve cervical cancer screening are needed. The aim of this study was to determine if self-collected HPV testing and results counseling improved Pap test completion by 6 months among women with HIV. Our results showed no difference in Pap test completion between the group who received HPV testing results and those who did not receive HPV testing and results counseling. There was also no difference between women who were HPV positive and those in the control group. To our knowledge, there are no other studies of the response of women with HIV to HPV test results and subsequent follow up. While population-based studies of women who were not participating in cervical cancer screening showed high rates of Pap test follow up for HPV-positive women, (40-43) these were large cervical cancer screening studies of hard-to-reach women. While description of procedures in these studies do not specify the type of counseling given to HPV-

negative women, it is reasonable to conclude that women who were HPV negative may not have receive the same strong encouragement to attend Pap testing as they did in the present study. Also there is no indication that women in these studies had HIV or other known risk factors for lower rates of Pap testing such as substance abuse. (48)

In this study, all women received the same counseling about the importance of Pap testing. Thus counseling (with incentive gift cards) may have been the effective intervention. The control group received enhanced care compared to what is received by the general clinic population, specifically gift cards, with counseling about HPV and the importance of Pap testing as part of the informed consent process, and reminder phone calls with an additional interview follow-up and second gift card. The ethical concern for clinical equipoise drove the creation of enhanced usual care for the control group in this study, and it may have washed out treatment effects that might have been observed from HPV self-collection and results counseling. In support of this possibility is the impressive increase in completion of pap screening across both study groups. Within the first six months of the baseline visit, over 35% of the entire sample completed Pap testing. Calculating crude Pap test completion rates, 90 women with available previous Pap dates completed Pap testing within 204 months, with a rate of 5.3 completed Pap tests per year. In this study, 35.2 Pap tests were completed within six months, leading to a rate of 70.4 completed Pap tests per year.

Among this study's strengths was that it was a randomized controlled trial, and it was powered appropriately to detect a clinically significant difference of 30% in Pap test completion and allowed enough participants to perform a multiple logistic regression with up to 9 factors. There was not enough power, however, to detect smaller differences in Pap testing that might have interesting scientific implications that are less important clinically. There was excellent

follow-up of over 91% of participants by telephone. In addition, use of medical records review as an outcome measure allowed for complete measurement of Pap test completion. Even if some women eventually had Pap tests at other locations, there is no reason to believe that this was different for the three groups.

The major limitation to this study was the fact that it was conducted in a single clinic with a relatively homogeneous patient population who were attending a clinic appointment. Thus, results may not be generalizable to other patient populations, such as women approached for HPV self-collection by a health worker during a home visit. The women in this study seem particularly resistant to other cues to action, such as monetary incentives. Thus HPV self-collection and results counseling might be effective among a different group of women, or in a different setting.

Another issue that might have impacted the study outcomes was the rollout of a new electronic medical record (EMR) during the study enrollment period. For two months during the study, availability of both HIV and gynecology appointments was limited in order to allow staff to learn the new system. This had no differential effects on intervention and control groups, so there was no threat to internal validity of the study. However, it is reasonable to consider that women might not have been able to make and appointments within the 6-month follow up period. Thus it is likely that a longer Pap test follow-up period (such as 12 months) would be necessary to fully evaluate the rate of Pap test completion.

There is much interest in self-collected specimens as a means to increase screening coverage and empower patients to participate in their own care. This study is the first, to our knowledge, to study the link of HPV self-collection to follow-up Pap testing. The lack of relationship between the intervention and follow-up care brings into question the effectiveness of

broadening access to HPV self-collection tests given our findings that patients may not use the information to pursue appropriate follow up care.

On the other hand, our low refusal rate of 5% indicates that self-collection of vaginal specimens for HPV is feasible in an HIV primary care setting. Women were quite willing to engage in self-collected HPV testing, and reported no serious problems completing the tests. The high acceptability of self-collected HPV tests even in this group of high-risk women remains important as HPV test technology continues to improve. Arbyn et al.'s 2014 meta-analysis (49) of accuracy of self-collected HPV versus clinician-collected samples showed similar sensitivity for high grade cervical lesions when polymerase chain reaction (PCR)- based tests were used. The PCR-based Roche Cobas HPV test was recently approved by FDA for primary cervical cancer screening (50) and thus could be considered for use to improve screening coverage for high-risk women who otherwise are not participating in cervical cancer screening recommendations. If PCR-based HPV screening were used as primary cervical cancer screening for women with HIV, this and other studies suggest that it would be possible to achieve very high rates of screening in this underserved population.

Implications for future research

It is clear from these findings that more research should be done into the reasons for inadequate participation in Pap testing among women with HIV. While no individual or combination of measured factors seemed to contribute to completion of Pap testing, it is clear that there are many factors that might affect women's ability or willingness to follow through on screening recommendations of all kinds. In Pap testing, the invasive nature of the test may hinder women's willingness to participate on a regular basis. In addition, comorbid conditions, common in HIV patients as they age (51) may affect ability and willingness to attend referral visits and follow up

on the increasing number of medical conditions that appear as patients live with HIV longer. Qualitative interviews with women about their specific clinical, personal and family situations may provide much needed clarification of ways in which clinicians can better respond to their needs. In addition, consideration of structural effects on care, like appointment availability and caregiver efforts to encourage patient follow up, might also provide useful information in how to improve both access to and utilization of available care.

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Figure 1: CONSORT flow chart.

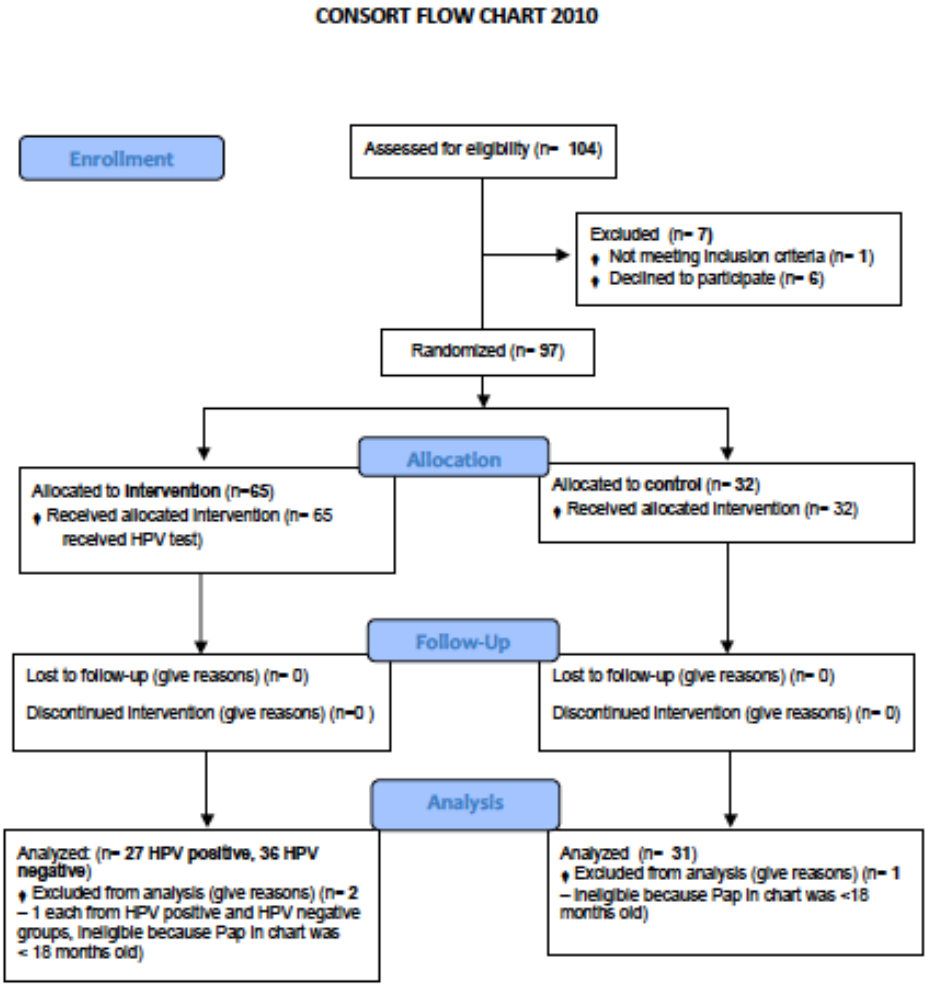


Table 1: Inclusion/Exclusion Criteria.

Inclusion criteria	**Exclusion criteria**
HIV infection	History of hysterectomy
Attend Adult HIV Clinic primary HIV care appointment	Currently pregnant
18 months or more since Pap test	
Speak & read English	
Eligible for cervical cancer screening	
Plans to have Pap testing at Johns Hopkins Hospital	

Table 2: Pap test completion outcome results, by groups

Group	Pap test completion, proportion (%)	Difference in Pap completion	p-value
HPV positive v. HPV negative	10/27 (37.0%) 11/36 (30.5%)	6.5%	0.30
HPV positive v. Control	10/27 (37.0%) 12/27 (38.7%)	- 1.7%	0.55

Table 3: Demographic and other participant characteristics.

Characteristic	**Entire sample Mean with SD or Number with Percent N = 94**	**Control n = 31**	**HPV - n = 36**	**HPV + n = 27**	**p-value**
Age	48.7 years (9.4)	48.6 years (SD 9.1)	49.5 years (SD 9.0)	47.8 years (SD 10.6,)	0.69 *
Education	11.6 years (2.3)	11.6 years (SD 3.2)	11.8 years (SD 1.8)	11.5 years (SD 1.8)	0.96 **
Race	Black 84.0% White 13.8% American Indian/Alaska Native 1 (1%) Asian 1 (1%)	29 (94%) Black	31 (86%) Black	19 (70%) Black	0.09 ***
Ethnicity	Hispanic 1 (1%) Non-Hispanic 93 (98.9%)	0	1	0	not calculated
History of substance abuse	49 (52.1%)	15 (48%)	17 (47%)	17 (62%)	0.41 #
CD4 count in study period	581.2 cells/mL (348.1)	653.3 cells/mm3 (SD 388.9)	600.1 cells/mm3 (SD 346.4)	473.4 cells/mm# (SD 280.5)	0.09 **
Viral load low in study period (<500 copies/mL)	78 (82.9%)	27 (87.1%)	31 (86%)	20 (74%)	0.38 #
CD4 nadir (lowest in chart)	216.6 cells/mL (174.0)	190 cells/mm3 (176.3)	231 cells/mm3 (231.2)	228.0 cells/mm3 (207.8)	0.60 ++
Months since previous Pap test (n = 90)	42.7 months (34.2)	35.9 (3.36)	48.6 (6.68)	40.6 (9.14)	0.76 **
Insurance type	Public 71 (75.5%) Private 14 (14.9%) Self-Pay 9 (9.6%)	Public 23 (74%) Private 3 (10%) Self-pay 5 (16%)	Public 26 (72%) Private 8 (22%) Self-pay 2 (5%)	Public 23 (81.5%) Private 3 (11%) Self-pay 2 (7%)	0.41 ***
History of previous abnormal Pap (n=71)	13 (18.3%)	6 (8.5%)	2 (2.8%)	5 (7.0%)	**0.04** ***
Household income <$20,000	70 (74.4%)	24 (77.4%)	24 (67.0%)	22 (82.0%)	0.66 ***

* Linear regression
** Kruskal Wallace test for non-normally distributed data
*** Fisher's Exact Test for small cell size
# Chi square
++ ANOVA

Table 3: Bivariate analyses of demographic and other characteristics with Pap test outcome

Characteristic N = 94	**Odds ratio (95% CI)**	**p-value**
Age	0.99 (0.95-1.04)	0.84
African American race	1.10 (0.34 -3.5)	0.88
Education	1.13 (0.93-1.38)	0.224
Insurance	Public 1.79 (0.34-9.27) Private 3.50 (0.53 - 23.1) Self-pay reference	0.49 0.19
Viral load<500	2.771 (0.712-10.3)	0.14
CD4 count	1.00 (0.99-1.00)	0.45
Household income <$20K/yr	0.87 (0.33-2.3)	0.78
Received other incentive	0.92 (0.2 - 3.9)	0.91
Number of months since last Pap	0.99 (0.98 - 1.01)	0.385
More than 42 months since last Pap	0.72 (0.26 - 1.97)	0.52
Previous pap abnormal (n=71)	0.63 (0.17 - 2.28)	0.482
Treatment group (control, HPV negative, HPV positive)	1.34 (0.46 – 3.92)	0.59

CHAPTER FOUR: MANUSCRIPT THREE:

TITLE: EFFECT OF TESTING HPV POSITIVE ON PERCEIVED THREAT OF CERVICAL CANCER AMONG WOMEN WITH HIV

Target journal: *Psycho-Oncology*

ABSTRACT

Objective

Women living with HIV are at higher risk for cervical cancer than other women, but many do not have adequate cervical cancer screening. Health Belief Model (HBM) concepts have been shown to be successful in predicting cancer screening. As part of the model, perceived threat of cervical cancer may be a reasonable factor in women's decision to seek cervical cancer screening, but has not been shown to be associated with screening behaviors. It is unknown whether the use of a biomarker for cervical cancer risk—such as oncogenic HPV—would increase perceived risk of cervical cancer in women with HIV, and subsequently prompt the women to complete cervical cancer screening with Pap tests.

Methods

This was an analysis of a subgroup of women who received HPV test results as part of a randomized controlled trial of self-collected HPV testing and results counseling. Eligible participants were women over age 18, with HIV infection, attending a primary HIV care visit, whose last Pap test occurred 18 months or more from the baseline visit date. Women enrolled in the study completed the Perceived Threat subscale of the Champion HBM Scale, modified to reflect cervical cancer and Pap testing, at a baseline visit, and again 3-5 weeks later. Results were analyzed using descriptive statistics, ANOVA, ANCOVA, and multiple linear regression.

Results

A total of 94 women were enrolled in the study; 63 of the participants were randomized to the HPV self-collection and results counseling group. Among the 63 women with HPV tests, 36 were negative, and 27 were positive. In adjusted analyses, women with a positive HPV result had increased Perceived Threat scores (β = -2.871137, $p<0.05$). Neither HPV positivity nor

Perceived Threat scores were associated with completion of follow-up Pap testing within 6 months of the baseline visit.

Conclusion

HPV positivity was associated with a statistically significant increase in perceived threat of cervical cancer in a group of women living with HIV who were late for Pap testing. HPV positivity was not related to an increase in Pap test attendance.

INTRODUCTION

For women living with human immunodeficiency virus (HIV), cervical cancer (CC) is an acquired immunodeficiency syndrome (AIDS)-defining illness. The prevalence of HPV infection among women with HIV is often high, and because of persistent high-risk HPV infection, the rates of invasive CC are 4 to 5 times higher for women with HIV than for other women [1]. Despite their higher risk for cervical cancer, many HIV-positive women do not have annual Pap testing as recommended. Importantly, HIV-positive women who receive screening and follow-up have rates of CC that do not exceed that of HIV-negative women [2]. The literature shows that women do not have annual Pap testing because they dislike the examination, feel embarrassed, fear the exam because of pain or discomfort, don't understand why they are at higher risk, or lack access to services [3,4,5]. Women also report not having regular Pap screening because they experience the gynecologic exam as negative, do not understand its significance or why they are at risk, or prefer not having a male provider [6]. Many interventions have focused on increasing cervical and other cancer screening by improving access to care [7].

One challenge in cancer screening is how to encourage utilization of existing screening programs. The Health Belief Model (HBM) was developed in the 1950's by the U. S. Public Health Service to explain how people utilize available health screening tests [8]. The first studies were concerned with finding out why people chose to engage in screening for tuberculosis or how people sought vaccination for polio. The basic version of the model includes two types of variables: those corresponding to the psychological readiness of a person to take action regarding a health state, and others corresponding to the degree to which the action in question is believed to be beneficial [9]. The main constructs include perceived susceptibility, benefits and barriers to

screening, perceived severity of illness, and self-efficacy. Cues to action are triggers for people to complete screening.

HBM-based interventions utilizing risk counseling to increase patients' perceptions of risk for breast cancer have improved mammography adherence, particularly among African-American women [8,10]. Risk counseling utilizing personalized risk assessments was also shown to increase short-term adherence to colorectal cancer screening [11]. A recent randomized trial demonstrated that education focused on HPV testing and follow-up significantly increased Pap test follow-up for women with a history of abnormal Pap tests [12]. Large European studies of women who did not respond to invitations for cervical cancer screening programs show that offering HPV self-collection and results increased screening participation rates overall, and that women who tested positive for HPV followed up with Pap testing at very high rates: 80% to 95% [13-15]. Qualitative research has found that women with HIV report that motivation to follow up after an abnormal Pap test is related to understanding their increased risk for cervical cancer, personal relationships with clinical staff, and being directly involved in their own care [16]. Conversely, Bish et al. (2002) and Tracy et al. (2010) demonstrated no relationship between HBM concepts of perceived threat and completion of Pap testing among women without HIV [17,18].

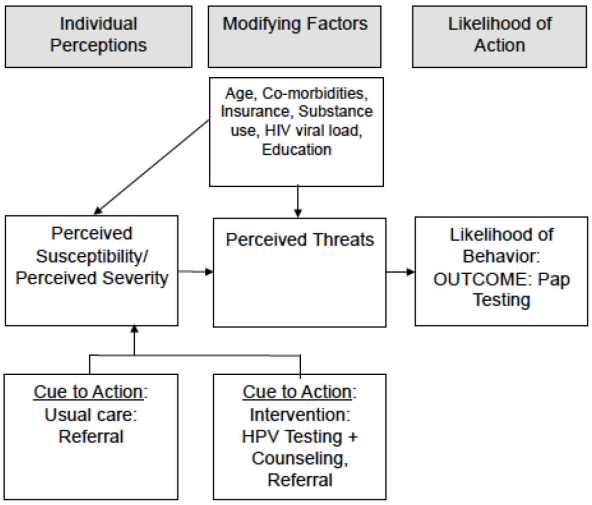
In this study, we tested whether self-collected HPV testing and results counseling would impact risk perception and attendance at cervical cancer screening among women at high risk for cervical cancer. HPV DNA testing has been used in cervical cancer screening since 2004 and is within the standard of care for screening women over age 30 [19]. Its optimal use in cervical cancer screening algorithms for women with HIV is unclear at this time [20]. There has been much interest in testing vaginal HPV self-collection strategies as a way to increase screening for

cervical cancer among underscreened populations. A recent meta-analysis of self-collected HPV specimens demonstrated good sensitivity of 0.85 (97% CI 0.81-0.90) for high-grade cervical lesions using the Qiagen Hybrid Capture 2 test. (21) Another study showed a high level of participation among women offered self-collection in a primary care setting. (22) Therefore, a self-collected high-risk HPV test offered by clinicians in an HIV primary care visit could provide such high-risk women with an accurate message of their risk for cervical cancer. This intervention was designed as a cue to action to increase women's knowledge of their risk for cervical cancer, utilizing a biomarker test that they could perform privately without a pelvic exam. A positive result would provide the women with an accurate message of their risk for cervical cancer.

We theorized that the self-collected HPV test result would help women achieve a more accurate perception of their risk for cervical cancer by increasing their perception of susceptibility to and severity of cervical cancer. These two constructs are combined as perceived threat, incorporating both perceptions of one's own risk and of the seriousness of the disease. Higher perceived threat is theoretically associated with increased likelihood of screening [8, 23].

(Insert Figure 1 about here)

Figure 1. HBM with HPV self-collection and results counseling as a cue to action. (8)



Thus, the HBM construct of perceived threat may be helpful in understanding the mechanism by which self-collected HPV tests and results counseling could help increase women's adherence to Pap testing.

The purpose of this analysis was to examine the perceived threat of cervical cancer in a cohort of women living with HIV, and to determine whether HPV testing and results counseling caused any changes in women's perceptions of threat or in completion of their follow-up Pap testing.

METHODS

The study took place at an adult HIV care practice at a large hospital in Baltimore, Maryland. This clinic has provided HIV specialty care to approximately 3,500 adults over 25 years of age. In 2009, approximately 900 of the clinic's patients were women.

On each day that an eligible woman had an appointment, the clinician seeing the woman was requested to give the woman information about the study and contact information for the researcher. When women expressed interest in the study, they were asked if they wished to participate in a study about cervical cancer screening using a self-collected vaginal sample for HPV. To facilitate follow-up, the researcher ensured that participants had access to a phone, and obtained multiple contact numbers and best times to reach them. Women were offered a $15.00 gift card for completing the baseline visit. At the baseline visit, the researcher interviewed women with a demographic survey and administered the Perceived Threat subscale of the modified Champion HBM scale [23], entering all data directly into a database administered by REDCap [24]. At two weeks after the baseline visit, the researcher contacted the participants for HPV results counseling. To encourage retention, participants were offered an additional $20 gift card to complete the follow-up phone call at three to five weeks. During that phone call, they completed the Perceived Susceptibility and Severity scale by interview with the researcher.

Champion HBM scale

The Champion HBM Scale was designed to measure HBM-related constructs in relation to breast cancer [23]. Recent studies used a modified scale to measure the same constructs in relation to cervical cancer and Pap testing by replacing breast cancer and mammography with cervical cancer and Pap testing in test items [17, 18, 25]. Items were rated on a 5-point Likert-type scale (from 1 = strongly disagree to 5 = strongly agree); responses within the scale were summed. The range of possible scores was 10 to 50. A lower score indicated a higher Perceived Susceptibility to and Perceived Severity of cervical cancer and a higher likelihood of screening.

Study variables

Demographic characteristics were measured through self-report during participant interviews, except for insurance status, which was obtained through medical record abstraction. Age and educational levels were measured in years to the date of the baseline visit. Race and ethnicity were categorical variables: Black, White, American Indian/Alaska Native, Asian, and Hispanic/non-Hispanic. Household income was a categorical variable (<$20,000/year, $20,000-$29,999/year, $30,000-$39,999/year, $40,000-$49,999/year, <$50,000/year).

Medical record abstraction via electronic medical records was completed six or more months after the baseline visit for a history of substance abuse, CD4 count, CD4 nadir, viral load, months since previous Pap test, and insurance type. History of substance abuse was entered into the database as a dichotomous variable, and reflected any history of substance abuse in the chart. CD4 count was measured in cells/mL and entered as the level recorded closest to the baseline date during the 6-month study period, if available. Viral load was measured in HIV RNA copies/mL and noted as the level recorded closest to the baseline date during the 6-month study period, if available. CD4 nadir was the lowest CD4 count in cells/mL found in the chart. Pap test results were recorded if the Pap test was available in the chart. Highly active antiretroviral

therapy (HAART) was recorded as a dichotomous variable, indicating that at the time of the baseline visit the participant was taking highly active antiretroviral medication.

Statistical methods

Summary statistics included calculation of means and standard deviations for continuous variables, and numbers and percentages for categorical variables. Differences between group means were tested using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test if the outcome variable was not normally distributed. Differences between groups on categorical variables were tested using one-way ANOVA. Differences between groups on dichotomous variables were tested using chi-square. Relationships between participant demographic and clinical characteristics and the Perceived Threat outcome were tested using analysis of covariance and linear regression. Reliability of the scale in this study was measured by calculating Cronbach's alpha of baseline and follow-up scores, and by completing a test-retest analysis of control group participants' scores.

RESULTS

Baseline data

Demographic characteristics of the 63 women in the HPV self-collection group are listed in Table 1.

(Insert Table 1 about here)

Study participants were primarily African-American (79%) and low income, with 73.0% reporting a household income of under $20,000 per year. The majority had public medical insurance (Medicaid or Medicare, 76.2%). The sample had a mean age of 48.8 (SD 1.2) years and had completed an average of 11.7 (SD 0.23) years of education. Most (68.2% SD 6%) had

an undetectable viral load; the mean CD4 cell count was 550.6 (SD 41.1) cells/mm3 and 95.2% were taking HAART. Over half (54.0%) of women reported a history of substance abuse.

Reliability of the Perceived Threat scale of the modified Champion HBM measure

Test-retest reliability was assessed by comparing pre- and post-test scores of the Perceived Threat scale from the control group. Canonical correlation analyses of the two scales showed excellent test-retest reliability of 0.9675. Cronbach's alpha for the pre-baseline was 0.7802, and 0.6962 for post-baseline, demonstrating acceptable internal consistency. Eighty-five of the 94 women completed follow-up Perceived Threat scales for a follow-up rate of 90.4%. The nine women who were lost to follow-up were significantly more likely to have a lower CD4 count, a higher viral load, and a history of substance abuse. Because of this, multiple imputation using linear regression modeling with these demographic variables was used to estimate follow-up mean Perceived Threat scores.

Perceived threat scores at baseline and at follow-up

At baseline, the HPV-negative group had a mean Perceived Threat score of 30.98 (SD 0.93); the HPV-positive group score was 30.89 (SD 1.43). At follow-up, the HPV-negative group's mean Perceived Threat score was 31.72 (SD 0.96); the HPV-positive group's score was 28.64 (SD 0.93).

Predictors of baseline score

Demographic and health factors were tested for independent effects on baseline Perceived Threat scores. The only factors that were significantly associated with more perceived threat at baseline were CD4 nadir and history of substance abuse. Results are summarized in Table 2.

A multiple linear regression of CD4 nadir and substance abuse history on the baseline Perceived Threat score showed significant effects for both CD4 nadir (0.01, $p < 0.05$) and substance abuse history (-3.27, $p < 0.05$). An interaction term of CD4 nadir * substance abuse history entered into the regression equation was not significant, demonstrating independent relationships of the variables with the baseline Perceived Threat score. Other factors such as age, education, African-American race, viral load, CD4 cell count, and current history of taking antiretroviral medication (HAART) were not associated with the level of baseline Perceived Threat score.

Effect of a positive HPV test on outcomes

Analysis of covariance with the baseline Perceived Threat score, HPV positivity, CD4 nadir and history of substance abuse variables showed a significant increase in perceived threat for HPV-positive women when controlling for the baseline score ($F = 8.8$ $p < 0.05$). Factors with a p-value of less than 0.4 were entered into a multiple linear regression model controlling for Perceived Threat baseline scores. This showed a significant increase in follow-up Perceived Threat scores for the HPV-positive group (see Table 3).

(Insert Table 3 about here)

There was no statistically significant relationship between baseline or follow-up Perceived Threat scores and completion of Pap testing by 6 months after the baseline (OR 0.97 SE 0.04 $p = 0.41$, and OR 0.97 SE 0.05 $p = 0.6$, respectively). Neither was there a statistically significant

increase in Pap testing for women testing HPV positive (OR 1.34, SE 0.7 p = 0.6). There was also no statistically significant difference in Pap test completion within 6 months between women who tested HPV negative (30.5%), and HPV positive (37.0%) (Test of proportions, p = 0.295).

DISCUSSION

The results from our study demonstrate that testing HPV positive resulted in increased perceived threat of cervical cancer among women with HIV as measured by a modified Champion HBM scale, but neither a positive HPV test nor the level of Perceived Threat score resulted in an increased rate of Pap testing within 6 months. This is in contrast to European population studies of self-collected HPV testing, which demonstrated high follow-up Pap testing rates for women testing HPV positive: 81.0% (13), 90.4% (14) and 100% [15]. It is likely that the women in these studies were not living with HIV in high numbers; they were identified only as non-attenders in regional cervical cancer screening programs. It is also reasonable to assume that investigators made efforts to recruit HPV-positive women into follow-up care, and did not attempt to reach women who tested negative for HPV. In our study, all women were advised to have follow-up Pap tests, and received special education regarding HPV through the informed consent process. This may explain the findings in our study, where the sense of perceived threat was heightened by the HPV test, but all women received consistent advice to follow up and then followed up in similar rates.

Our study findings are consistent with the reviewed literature on cervical cancer screening and perceived threat of cervical cancer. In Bish et al.'s 2002 study of prediction of cervical cancer screening using the HBM and Theory of Planned Behavior, the Champion HBM

Scale's perceived susceptibility and perceived susceptibility subscales were not associated with follow-up Pap testing 3 months after measurement [17]. A retrospective study of a group of lesbian women by Tracy et al. (2010) showed no relationship between the Champion HBM Scale's perceived susceptibility and perceived susceptibility subscales and reported history of Pap testing within the previous 24 months [18]. These studies did not involve biomarkers as in our study; nevertheless, it appears that perceived threat of a health condition does not, alone, predict cervical cancer screening behavior.

Among this present study's strengths was that this randomized controlled trial took place in a clinical care unit in a busy hospital, and was designed to mimic as closely as possible the situation of actually using a self-collected HPV test in a real-world setting. The study was powered to allow enough participants to perform a multiple linear regression with up to six factors, using the general guideline of 10 participants per factor. There was excellent follow-up of over 91% of participants by phone. In addition, use of medical records review as an outcome measure allowed for complete measurement of Pap test completion. Even if some women eventually had Pap tests at other locations, there is no reason to believe that this was different for HPV-positive or negative women.

The study's limitations include possible loss to follow-up for Pap tests done unexpectedly at clinics to which the study team did not have access. In addition, the study was powered to detect a rather large, clinically significant difference in Pap testing (30%) between HPV positive and control group women, with enough participants to allow multiple regression analyses. It is likely that it was not adequately powered to detect smaller but important effect sizes.

A major limitation to this study was the fact that it was conducted in a single clinic with a relatively homogeneous patient population who were attending a clinic appointment. Thus,

results may not be generalizable to other patient populations, such as women approached for HPV self-collection by a health worker during a home visit. The women in this study seem particularly resistant to other cues to action, such as monetary incentives; just as Perceived Threat as a construct did not result in increased Pap testing in this group, neither did rewards triggered by being late for Pap testing.

Women with HIV are bombarded with health information. It is possible that a positive HPV test result increased women's perception of risk of cervical cancer, but competed with too many other risk messages they receive about their health. For women living with HIV, completing a Pap test may not be a high priority. Another possible explanation for the lack of relationship between testing HPV positive and completing Pap testing is that despite the consent process—which included basic information about HPV and its connection to cervical cancer—women in our sample still did not understand enough about HPV to properly evaluate their risk and take action.

It is clear that women with HIV have many competing priorities—low income, complex HIV-related medical issues and complicated family situations—that cervical cancer screening may be considered relatively unimportant. Indeed, Roman et al.'s 2014 study of non-HIV infected, underserved Black, Latina and Arab women in Dearborn, Michigan found that cervical cancer screening in Black women was lower among those reporting higher scores for "competing priorities," a score combining needing to work two jobs, having low household income, and needing to reschedule multiple appointments [26]. Examining medical comorbidities would get at this issue in this sample, but so would be measuring more factors related to psychosocial stressors such as work, low income, active substance abuse, and caring for parents or young grandchildren. A multi-level ecological model would be most appropriate for this kind of

analysis, one that could incorporate individual-level factors such as HBM concepts, but also include women's experiences in their medical practices and communities at large. For example, literature has shown that, especially for African-American women in general, counseling and targeted education increases participation in cervical cancer screening [7]. The patient retention in HIV care literature indicates that improving communication in the patient-clinician relationship can increase engagement in HIV care, improving HIV-related health overall [27].

In closing, we must ask this question: Why be concerned about perceived threat of cervical cancer? There is ample evidence that this does not, by itself, predict patient follow-up to cervical cancer screening. However, such results are delivered to patients every day in clinical practice. Since this study was designed to mimic an intervention that could take place in a real clinic, its results have profound implications for practice. It is imperative that as clinicians we reconsider our usual way of handling screening test results with patients, particularly those who live in challenging urban communities with multiple, pressing social problems. Those of us who seek to reach and prevent illness in the most vulnerable people need to remember that handing out laboratory or other results in ever-shorter patient care visits is fraught with challenges—not the least of which is that patients may not be able to appreciate their own risk for illness, or may not be able to access appropriate follow-up care that at least appears to be available in the appointment books and insurance rolls. Making cervical cancer screening easier for women is the first step; we must also make sure that the results obtained are meaningful and that the next step in screening is clear and reasonable for women to participate in, no matter how complicated their lives are.

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Table 1. Demographics and other characteristics of sample.

Characteristic	HPV self-collection group Mean with SD or Number with Percent n = 63	HPV- n = 36	HPV+ n = 27	p-value
Age	48.2 years (1.2)	49.5 years (SD 9.0)	47.8 years (SD 10.6,)	0.69 *
Education	11.7 years (0.2)	11.8 years (SD 1.8)	11.5 years (SD 1.8)	0.96 **
Race	Black 50 (79.4%) White 11 (17.5%) American Indian/Alaska Native 1(1.5%) Asian 1(1.5%)	31 (86%) Black	19 (70%) Black	0.09 ***
Ethnicity	Hispanic 1 (1.5%) Non-Hispanic 62 (98.9%)	1	0	not calculated
History of substance abuse	49 (53.952.1%)	17 (47%)	17 (62%)	0.41 #
CD4 count in study period	581.2 cells/mL (348.1)	600.1 cells/mm3 (SD 346.4)	473.4 cells/mm# (SD 280.5)	0.09 **
Viral load undetectable (<20 copies/mL)	43 (68.2%)	26 (72%)	17 (63%)	0.38 #
CD4 nadir (lowest in chart)	216.6 cells/mL (174.0)	231 cells/mm3 (231.2)	228.0 cells/mm3 (207.8)	0.60 ++
Months since previous Pap test (n = 90)	42.7 months (34.2)	48.6 (6.68)	40.6 (9.14)	0.76 **
Insurance type	Public 71 (75.5%) Private 14 (14.9%) Self-Pay 9 (9.6%)	Public 26 (72%) Private 8 (22%) Self-pay 2 (5%)	Public 23 (81.5%) Private 3 (11%) Self-pay 2 (7%)	0.41 ***
Household income <$20,000	46 (73.0%)	24 (67.0%)	22 (82.0%)	0.66 ***

* Linear regression
** Kruskal-Wallace test for non-normally distributed data
*** Fisher's Exact Test for small cell size
# Chi square
++ ANOVA

Table 2. Relationship between characteristics and baseline Perceived Threat score

History of substance abuse	β = -3.12 p = 0.05
HPV positive	β = -0.08 p =.96
Age	β = 0.07 p = 0.40
Education	β = -.18 p = 0.69
African-American race	β = -0.08 p = 0.97
log Viral load	β = -0.12 p = 0.68
CD4 count	β = -0.01 p =0.75
Income	No difference among categories p > 0.5
CD4 nadir	**β = 0.01 p = 0.04**
HAART	β = -2.15 p = 0.51

Table 3. Bivariate analyses of effects on Perceived Threat outcome

History of substance abuse	**β = -2.99 p = 0.03**
HPV positive	β = **-3.08 p < 0.05**
Age	β = 0.01 p = 0.90
Education	β = 0.47 p = 0.24
African-American race	β = -1.58 p = 0.36
log Viral load	β = -0.19 p = 0.45
CD4 count	β= 0.00 p =0.92
Income	No difference among categories p > 0.5
CD4 nadir	β = 0.00 p = 0.98
HAART	β = -4.13 p = 0.21

Table 4. Final multiple linear regression model adjusting for baseline perceived threat score

Characteristic	Final adjusted analysis, with coefficient &and p-value
History of substance abuse	β = -0.66 p = 0.54
HPV positive	**β = -3.08 p < 0.05**
Education	β = 0.47 p = 0.09
HAART	β = -1.32 p = 0.60
African American race	β = -2.10 p =0.10
CD4 nadir	β = -0.01 p =0.07

CHAPTER FIVE: DISCUSSION

INTRODUCTION

Self-collected HPV testing and results counseling could be utilized in the HIV primary care setting to promote Pap testing among women with HIV. This dissertation study was a randomized trial to test whether receiving self-collected HPV testing and results counseling in HIV primary care would increase completion of Pap testing in a group of women attending the Johns Hopkins Hospital Adult HIV Clinic for HIV Care. The study used the HBM concept of Perceived Threat of cervical to test whether HPV testing and results would change perception of susceptibility to and severity of cervical cancer. Following HBM concepts, the HPV test and results counseling were cues to action that also correctly identify women at higher risk for disease. During the study, 94 women who were late for Pap testing were recruited for participation while they were at an HIV care appointment and were randomized to HPV self-collection and results counseling, or to be in a control group. At baseline women were interviewed with the Perceived Threat subscale of a modified Champion HBM scale, and then again after the HPV test result or Pap reminder phone call. Six months after enrollment, medical records were reviewed for completion of Pap testing in the intervening months.

SUMMARY OF FINDINGS BY AIMS

Aim 1

Self-collected HPV testing and results counseling did not improve Pap test attendance when compared the control group. Overall, 35% of the entire sample completed their Pap tests within 6 months of the baseline visit.

Aim 2

Women who tested positive for HPV had higher Perceived Threat scores at follow-up, controlling for the baseline score. However, higher Perceived Threat scores at follow-up were not associated with completion of Pap testing at higher rates. The follow-up interview rate for the Perceived Threat scale was 91%.

STRENGTHS AND LIMITATIONS

This was a randomized clinical trial conducted according to CONSORT group standards, powered to detect a clinically significant difference of 30% in Pap testing between groups. An excellent phone interview follow up rate of 91% was achieved, and the medical records review for final outcome measure allowed 100% follow up.

Limitations included the possibility of inadequate recording of Pap test and results in the patient chart. In addition, the study was not adequately powered to detect smaller differences in Pap testing rates that might have important scientific implications. The major limitation to this study was that it was conducted in a single clinic with a relatively homogeneous patient population who were attending a clinic appointment. Thus, results may not be generalizable to other patient populations such as women approached for HPV self-collection by a health worker during a home visit. The women in this study seem particularly resistant to other cues to action triggered by being late for Pap tests, such as monetary incentives from their insurance carriers. Thus HPV self-collection and results counseling might still be effective among a different group of women, or in a different setting.

IMPLICATIONS

Self-collection of cervico-vaginal cells for HPV testing was feasible in this population, as indicated by the 95% overall participation rate. The study overall acted as an intervention to promote Pap testing. High follow up rates overall demonstrated that intensive interventions to

improve cervical cancer screening can be effective in increasing cervical cancer screening participation in high risk women like those in the Clinic for Adult HIV Care at Johns Hopkins Hospital.

DISSEMINATION OF FINDINGS

These findings will be disseminated in target journals as listed, and in other publications should it become necessary.

RECOMMENDATIONS FOR FUTURE RESEARCH

Self-collection of vaginal specimens for cervical cancer screening remains a very attractive option to reach women who otherwise do not participate in regular cervical cancer screening programs. More research should be done to evaluate the possibility of using HPV self-collection for primary cervical cancer screening for women with HIV who do not engage in screening in the usual manner, and in optimizing its use to increase women's understanding and utilization of the results. In addition, more research needs to be done on women with HIV's understanding of the relationship between HPV and cervical cancer, and whether knowledge about HPV status would affect women's intention to participate in cervical cancer screening. Given that much fear surrounds the gynecologic exam, particularly among marginalized women such as patients in an Adult HIV Clinic, it is only reasonable to continue to search for alternatives to screening by Pap and vaginal speculum exam, even though the exam itself might yield clinical information that women might find helpful.

It is also interesting to consider a new framework that might address the broader context of women's lives and where cervical screening fits in. An ecological framework that can incorporate individual level frameworks, like that of HBM, plus other factors like institutional level factors, community and family contexts and societal pressures, would give a more realistic

picture of the challenges poor, urban women with HIV face when trying to manage their complex medical issues as they balance their lives.

CONCLUSION

Given that much fear surrounds the gynecologic exam, particularly among marginalized women such as patients in an HIV Clinic, it is only reasonable to continue to search for alternatives to screening by Pap and vaginal speculum exam, even though the exam itself might yield clinical information that women might find helpful. As technology improves, our confidence that self-collected HPV tests yield clinically reliable and useful information may lead to the opportunity to offer screening via self-collection to more and more women with HIV who are not receiving adequate cervical cancer screening. Women with HIV remain at higher risk for cervical dysplasia and cancer, despite living in the United States with enviably low rates of ICC when compared with the developing world. Utilizing all of the tools available to us would help us to better help women avoid cervical cancer, the most preventable cancer known.

APPENDICES

APPENDIX 1: INTERVIEW FORMS

NOTE: The interview data was entered directly into REDCap.

ID _____

Date _____

Demographic information questionnaire

1. What is your age? _____ years

2. What is your race? _____
Are you Hispanic/Latina? Yes/No

3. How many years of school did you complete?

4. Do you receive cash or another gift when you do your Pap test? Yes/No

Perceived Susceptibility and Severity Questionnaire

This is a short questionnaire about cervical cancer. Please answer how much you agree with the following questions. The answers are: 1 for strongly agree, 2 agree, 3 neutral, 4 disagree, 5 strongly disagree.

Five-point Likert Scale: **1 = strongly agree, 5 = strongly disagree**

1. It is likely that I will get cervical cancer in the future. [futurecan]

1 2 3 4 5

2. My chances of getting cervical cancer in the next few years are high. [chancecan]

1 2 3 4 5

3. I feel I will get cervical cancer some time during my life. [lifecan]

1 2 3 4 5

4. The thought of cervical cancer scares me. [scarecan]

1 2 3 4 5

5. When I think about cervical cancer, my heart beats faster. [heartcan]

1 2 3 4 5

6. I am afraid to think about cervical cancer. [afraidcan]

1 2 3 4 5

7. Problems I would experience with cervical cancer would last a long time. [longcan]

1 2 3 4 5

8. Cervical cancer would threaten a relationship with my boyfriend, husband, or partner. [relationcan]

1 2 3 4 5

9. If I had cervical cancer my whole life would change. [lifechangecan]

1 2 3 4 5

10. If I developed cervical cancer, I would not live longer than 5 years. [5yearcan]

1 2 3 4 5

3-5 week phone interview follow up – both groups

ID _____

Date _____

Perceived Susceptibility and Severity Questionnaire

This is a short questionnaire about cervical cancer. Please answer how much you agree with the following questions. The answers are: 1 for strongly agree, 2 agree, 3 neutral, 4 disagree, 5 strongly disagree.

Five-point Likert Scale: **1 = strongly agree, 5 = strongly disagree**

1. It is likely that I will get cervical cancer in the future. [futurecan]

1 2 3 4 5

2. My chances of getting cervical cancer in the next few years are high. [chancecan]

1 2 3 4 5

3. I feel I will get cervical cancer some time during my life. [lifecan]

1 2 3 4 5

4. The thought of cervical cancer scares me. [scarecan]

1 2 3 4 5

5. When I think about cervical cancer, my heart beats faster. [heartcan]

1 2 3 4 5

6. I am afraid to think about cervical cancer. [afraidcan]

1 2 3 4 5

7. Problems I would experience with cervical cancer would last a long time. [longcan]

1 2 3 4 5

8. Cervical cancer would threaten a relationship with my boyfriend, husband, or

partner. [relationcan]

1 2 3 4 5

9. If I had cervical cancer my whole life would change. [lifechangecan]

1 2 3 4 5

10. If I developed cervical cancer, I would not live longer than 5 years. [5yearcan]

1 2 3 4 5

Final Chart Review Form

ID _____

Date of final chart review _____

Date of baseline visit _____

Race per EMR _____

Was Pap in JHH record? (circle) Yes/No

Was it done within 6 months of baseline visit? (circle) Yes/No

If Pap was present, date of Pap _____

Result of Pap test _____

HIV viral load _____

Date of HIV viral load _____

CD 4 count _____

Date of CD 4 count _____

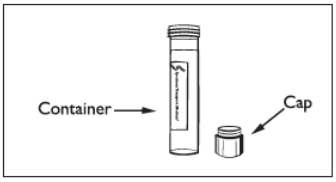
Insurance (circle): Public/Private/Self-pay

HAART (circle): yes/no

History of substance abuse (circle): yes/no

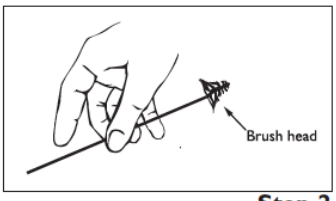
SPECIMEN SELF-COLLECTION PROCEDURE

1. Before you perform the specimen self-collection, prepare the transport container. Unscrew or pull out the cap and lay it with the inside of the cap pointing up. Being careful to not spill the liquid, place the container on a flat surface within reach, making sure that the container is steady.



Step 1

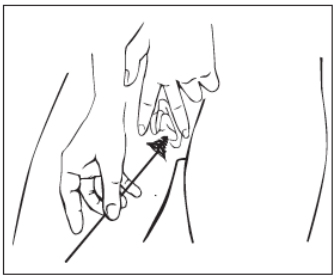
2. With your dominant hand (the hand you use to write), hold the plastic end of the brush so that the brush head is pointing toward you.



Step 2

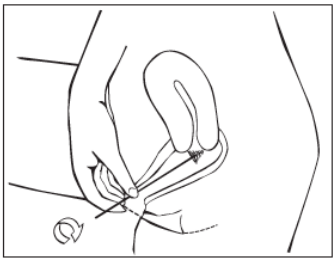
3. With your other hand, gently open the outside of your vagina and insert the tip of the brush into the opening. Point the tip of the brush toward your lower back.

4. Hold the brush steady and straight. Slowly and gently insert the brush into your vagina so that it follows the natural path of your vagina. If it does not slide easily, gently rotate the brush to the left or the right. If you experience lasting pain or major discomfort, stop and talk to the nurse or doctor.



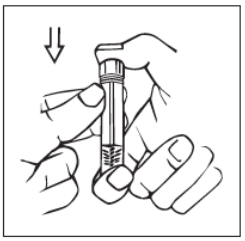
Steps 3 and 4

5. Continue to insert the brush until you meet resistance. This should be at least two to three inches. Once you meet resistance, gently hold the device in place for about 10 seconds and then turn the entire brush in a circle (like stirring) 3-5 times to remove cells from the cervix.



Step 5

6. Remove the brush from your vagina. Break the shaft by snapping it while holding firmly with one hand near the brush head and the other hand near the smooth end. Dispose of the handle. Put the brush head in the plastic transport container until the end of the brush touches the bottom of the container. Only the lower portion of the brush will be in the container and in the liquid. Screw on or push on the top tightly.



Step 6

courtesy of Dr. Patti Gravitt Study Visit Completion Form

ID number _____

Date _____

Group assignment (circle): Intervention/Control

HPV Test Completed? Yes/No

Time Interview started: _____

Time Interview ended: _____

Time HPV Self-Collection Explanation Started: _____

Time HPV Self-Collection Explanation Ended: _____

Time HPV Self-Collection Started: _____

Time HPV Self-Collection Ended: _____

Time HPV sample clinic processing started: _____

Time HPV sample clinic processing ended: _____

Comments on process (if in intervention, any problems with HPV collection? any issues with interview?)

The *Self*-Collection Study

Your patient may be eligible for this study of self-collected HPV tests!

She can see Jeanne Murphy today in:

Total possible incentive: ***$35*** for 1 short study visit and 2 phone call follow-ups

Jeanne Murphy, MSN, CNM
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Collaborators: Jason Farley, PhD, MPH, CRNP; Jean Anderson, MD; Hayley Mark, PhD, MPH, RN
IRB#: NA_00071156



Approved October 22, 2012

Flier announcing study and location of researcher

APPENDIX 2: ETHICAL APPROVALS

JOHNS HOPKINS
MEDICINE

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410-955-4367 Fax
e-mail: jhmirb@jhmi.edu

Date: May 24, 2012

NEW APPLICATION APPROVAL

Review Type:	Convened
PI Name:	Hayley Mark
Study #:	NA_00071156
Study Name:	A Test of an Intervention to Improve Pap Testing among Women with HIV
Committee Chair:	Joseph Carrese
Committee:	JHM-IRB 5

Date of review: May 21, 2012

Date of approval: May 21, 2012

Date of expiration: May 20, 2013

The JHM IRB approved the above-referenced New Application.

Date of Approval and Expiration Date: The approval and expiration date for this research are listed above. If the approval lapses, the research must stop and you must submit a request to the IRB to determine whether it is in the best interests of individual participants to continue with treatment interventions.

Changes in Research: All proposed changes to the research must be submitted using an eIRB Change in Research application. The changes must be approved by the JHM IRB prior to implementation, with the following exception: changes made to eliminate apparent immediate hazards to participants may be made immediately, and promptly reported to the JHM IRB.

Continuing Review: Continuing Review Applications should be submitted at least 6 weeks prior to the study expiration date. Failure to allow sufficient time for review may result in a lapse of approval. If the Continuing Review Application is not submitted prior to the expiration date, your study will be terminated and a New Application must be submitted to reinitiate the research.

Unanticipated Problems: You must inform the IRB of any unanticipated problems involving risks to participants or others.

If this research has a commercial sponsor, the research may not start until the sponsor and JHU have signed a contract.

Study documents:

Written Consent:

Only consent forms with a valid approval stamp may be presented to participants. All consent forms signed by subjects enrolled in the study should be retained on file. The Office of Human Subjects Research conducts periodic compliance monitoring of protocol records, and consent documentation is part of such monitoring.
FINAL_Mark NA_00071156_CF_052112_No Logo.doc

HIPAA Form 4:
FINAL_Mark_NA_00071156_HIPAA Form 4_052112_No Logo.doc

eFormA:
Murphy_eformA2-10-12-1.doc

Study Team Members:
Jean Anderson, Jason Farley, Jeanne Murphy

APPENDIX 3: LABORATORY PERMITS/APPROVALS

JOHNS HOPKINS
INSTITUTIONS

Biosafety Office
Health, Safety & Environment
2024 East Monument Street, Suite B-200
Baltimore, MD 21205-2223
(410) 955-5918 / FAX (410) 955-5929
www.hopkinsmedicine.org/hse

MEMORANDUM **April 17, 2012**

TO: **Dr. Hayley Mark**
Nursing
525 N. Wolfe Street, 449

FROM: Stephen C. Dahl, Ph.D., RBP
Biosafety Officer

SUBJECT: Registration of Infectious Agents and Pathogens

PROJECT TITLE: **A Test of an Intervention to Promote Pap Testing Among Women with HIV**

AGENT: **Cervico-vaginal samples from HIV positive patients**

IBC REGISTRATION: # **P1203290101** IBC APPROVAL DATE: **4/16/2012**

EXPIRATION DATE: **2/28/2013**

BIOSAFETY LEVEL: Facilities **2;** Practices **2**

The Johns Hopkins Institutional Biosafety Committee (IBC) has reviewed and approved the use of the infectious agent, pathogen, or potentially pathogenic material referenced above. Please retain this letter in your records as it represents your official notice that work associated with this proposal may now proceed. Any correspondence regarding this project should reference the IBC registration number above.

Laboratory inspections will be performed annually by HSE staff to assure compliance with the biosafety level assigned to your project. Non-compliant laboratories risk losing approval status. All faculty and staff who work with animals are required to present to Occupational Health Services (410.955.6211) for enrollment in the Animal Exposure Surveillance Program, (AESP). Faculty and staff using human materials such as blood, internal body fluids, unfixed tissues, and human-derived cell lines are required to attend annual Bloodborne Pathogen Exposure Control training (provided by HSE) as mandated by state and federal regulations. Personnel involved in the shipment of research materials must receive formal training in packaging and shipping to comply with federal Hazardous Materials Regulations. See the HSE website for details.

Infectious Agent/Pathogen Registrations expire one year from the date of issuance. An update form will be sent 30-60 days prior to the anniversary date of your registration. Please note any changes to your project, personnel, laboratory or office location, etc., and return the form to the Biosafety Office at the address above.

Please call (410) 955-5918 or email us at biosafety@jhu.edu if you have any questions about this research registration. We look forward to working with you.

JOHNS HOPKINS
INSTITUTIONS

Biosafety Office
Health, Safety & Environment
2024 East Monument Street, Suite B-200
Baltimore, MD 21205-2223
(410) 955-5918 / FAX (410) 955-5929
www.hopkinsmedicine.org/hse

MEMORANDUM **March 29, 2012**

TO: **Dr. Hayley Mark**
Nursing
525 N. Wolfe Street, 449
SON

FROM: Stephen C. Dahl, Ph.D., RBP
Biosafety Officer

SUBJECT: **Registration of Human Tissue--Clinical**

AGENT: **Human Tissues, Body Fluids, and Cell Lines**

JHU IBC REGISTRATION NO.: **BC1203290201** BIOSAFETY LEVEL: **1**

APPROVAL DATE: **3/01/2012** EXPIRATION DATE: **2/28/2013**

In accordance with OSHA Standards (29 CFR 1910.1030), the Biosafety Office of Johns Hopkins Institutions has registered your research projects for the Institutional Biosafety Committee (IBC). Please use this number in any correspondence you may have with us. The registration number above applies to **all** research projects involving human blood, internal body fluids, unfixed tissues, and cultured cell lines performed under your direction during the 12-month period following the date of issue. The Biosafety Office should be notified if changes in personnel are associated with your studies, however, **you are not required to submit registration forms for additional projects involving human materials unless you intend to introduce recombinant DNA or potentially infectious or pathogenic organisms into human subjects.**

This letter acknowledges human tissue and body fluid registration for use in IBC, IRB, IACUC, and research grant submissions. **Faculty and staff using human materials such as blood, internal body fluids, and unfixed tissue are required to attend annual Bloodborne Pathogen Exposure Control training (provided by HSE) as mandated by state and federal standards.** An annual update letter will be sent 30-60 days prior to the above expiration date and should be returned in a timely fashion to maintain this registration in good standing.

Please call (410) 955-5918 or email us at biosafety@jhu.edu if you have any questions about this research registration. We look forward to working with you.

JHU BIOSAFETY SECURITY CODE 2007

B E-Initial 12/06

APPENDIX 4: CURRICULUM VITAE

CURRICULUM VITAE

JEANNE MURPHY
MSN, CNM, PhD(c)

Address: 19805 Pinebark Way
Brinklow, MD 20862
Home: 301-774-0898
Mobile: 917-548-5426
Email: jmurph60@jhu.edu

EDUCATION:

2009 – present	**Doctor of Philosophy** (Ph.D.) anticipated, 2014 The Johns Hopkins University School of Nursing Baltimore, MD
2012	**Graduate Certificate in Health Disparities & Health Inequality** The Johns Hopkins University Bloomberg School of Public Health Baltimore, MD
1994	**Master of Science in Nursing** (M.S.N.) Maternal/Newborn Nursing/Nurse-Midwifery Certificate in Diabetes Care Yale University School of Nursing New Haven, CT
1992	**Associate of Science in Nursing** (A.S.N.) Springfield Technical Community College Springfield, MA
1985	**Bachelor of Arts** (A.B.) Comparative Literature: English/Spanish Brown University Providence, RI
1984	**GLCA Latin America Program in Bogotá, Columbia** Kenyon College Gambier, OH

TRAINING:

2013	**Certificates of Completion: Principles and Practices of Cancer Prevention and Control Course & Molecular Prevention Course** Division of Cancer Prevention National Cancer Institute National Institutes of Health Bethesda, MD
2011	**Certificate in First Assisting for Cesarean Birth** The Institute of Midwifery Philadelphia University Philadelphia, PA
2010	**Certificate of Completion: Meta-analysis** Institute of Nursing Science Summer School University of Basel Basel, Switzerland
1998	**Colposcopy Education** Cicatelli Associates/Columbia University College of Physicians and Surgeons New York, NY

CURRENT LICENSES AND CERTIFICATIONS:

2010 – present	Maryland Certified Registered Nurse-Midwife R189742
2010 – present	Federal DEA and Maryland CDS available upon request
1994 – present	New York Registered Nurse 463790-1
1994 – present	New York Licensed Midwife F000369-1
2005 – present	New York Nurse Practitioner in Women's Health F420874-1

PROFESSIONAL EXPERIENCE:

2013	**Clinical Research Clinician,** part-time Cervical cancer and sexually transmitted infection screening, primary care and wound care with IV drug users in Baltimore City.

Reproductive Health/Needle Exchange Program Baltimore City Health Department

2011 - present	**Certified Nurse-Midwife**, per diem Hospitalist midwifery practice. St. Joseph Medical Center**,** Towson, MD
2012 – present	**Faculty,** occasional Lectures for STD clinicians on HPV epidemiology and cancer screening. STD/HIV Prevention Training Center, Baltimore, MD
2008 – present	**Instructor,** online Taught undergraduate and graduate nursing courses. Mercy College, Dobbs Ferry, NY
2010 – 2011	**Certified Nurse-Midwife**, per diem Worked in prenatal clinic for uninsured women. Frederick Memorial Hospital, Frederick, MD
2003 – 2009	**Certified Nurse-Midwife/Women's Health N.P.** Full-scope midwifery practice including colposcopy. Hudson Valley Integrated Obstetrical Practice, Nyack, NY
2009	**Adjunct Instructor** Taught in Nurse-Midwifery and Nursing programs. New York University College of Nursing, New York, NY
2008	**Certified Nurse-Midwife/Women's Health N.P.** General gynecology and midwifery practice in Broadway Clinic, Allen Pavilion. Columbia-Presbyterian Medical Center, New York, NY
2007 – 2009	**Clinical Implementation Coordinator and Faculty** Taught CenteringPregnancy group prenatal care to various sites nationally. Provided consultation services to new CenteringPregnancy programs. Centering Healthcare Institute, Boston, MA
2007 – 2009	**Board Member** Assisted the New York State Board of Regents on matters of professional licensing and professional conduct for midwives. New York State Board of Midwifery, Albany, NY
1996 – 2003	**Certified Nurse-Midwife** Full-scope midwifery practice including colposcopy and CenteringPregnancy.

	Bronx-Lebanon Hospital Center, Bronx, NY
1994 – 1998	**Certified Nurse-Midwife** Full-scope midwifery practice. Wyckoff Heights Hospital Center, Brooklyn, NY
1994, summer	**Volunteer Registered Nurse** Obstetrical nursing at a birth center catering to Mexican farmworker women and their families. Holy Family Services Birth Center, Weslaco, TX
1993 – 1994	**Registered Nurse, Maternal/Child Health** Home visiting for high-risk women and their children. Visiting Nurse Association, New Haven, CT
1987 – 1991	**Research Assistant** Interviewer for large studies of psychiatric illness among teen substance abusers and among adult members of the National Collaborative Perinatal Project cohort. Harvard School of Public Health, Boston, MA Brown University Child Study Center, Providence, RI
1985 – 1987	**Counselor/Program Manager** Live-in staff at a program for mentally ill adults transitioning from long term hospitalization into the community. Alternatives Unlimited, Inc., Whitinsville, MA

HONORS AND AWARDS:

2013	**Mary Ann Shah New Author Award** *Journal of Midwifery & Women's Health*
2013	**Nursing Science Advancement Dissertation Grant Award** Council for the Advancement of Nursing Science/ Southern Nursing Research Society
2012	**National Research Service Award F31 NR013633** "A Test of an Intervention to Improve Pap Testing among Women with HIV." National Institute of Nursing Research National Institutes of Health
2010	***ThinkSwiss* Travel Grant** Institute of Nursing Science University of Basel Basel, Switzerland

2002	**Midwife of the Year Award** Bronx-Lebanon Hospital Center Bronx, NY
1998	**Fellowship in American Society for Colposcopy and Cervical Pathology**
1994	**Sigma Theta Tau International Honor Society of Nursing**, *Delta Mu* chapter Yale University School of Nursing New Haven, CT
1992	**Highest Honors** Springfield Technical Community College Springfield, MA

RESEARCH GRANTS:

June 2014	**Cancer Prevention Fellowship** National Cancer Institute National Institutes of Health
2012 – 2014	**National Research Service Award F31 NR013633** "A Test of an Intervention to Improve Pap Testing among Women with HIV." Advisor: Hayley Mark, PhD, MPH, RN National Institute for Nursing Research National Institutes of Health
2013	**Nursing Science Advancement Dissertation Grant Award** Council for the Advancement of Nursing Science/ Southern Nursing Research Society
2009 – 2012	**Health Disparities Fellowship T32 NR007968** The Johns Hopkins University School of Nursing

SCHOLARSHIP:

Publications: (* data-based)

* Coyne K.S., Margolis M.K., **Murphy J.**, Spies J. Validation of the UFS-QOL-hysterectomy questionnaire: modifying an existing measure for comparative effectiveness research. *Value Health*. 2012 Jul;15(5):674-9.

* Farley, J.E., Hayat, M.J., **Murphy, J**., Sheridan-Malone, E., Mark, H., & Anderson, J. Knowledge, Attitudes and Practices of OB/GYN Nurses and Auxiliary Staff in the Care of Pregnant Women Living with HIV. *J Assoc Nurses AIDS Care.* 2013 Jul 19. pii: S1055-3290(13)00085-X. doi: 10.1016/j.jana.2013.04.004.

Murphy J., Mark H. Cervical Cancer Screening in the Era of Human Papillomavirus Testing and Vaccination. *J Midwifery Womens Health*. 2012 Nov-Dec;57(6):569-76. doi: 10.1111/j.1542-2011.2012.00207.x.

* **Murphy, J**., Samples, J., et al. "They talk like that, but we keep working": Sexual harassment and sexual assault experiences among Mexican Indigenous farmworker women in Oregon. *Journal Immigrant Minority Health.* Feb11 2014 (Epub ahead of print).

* Paterno, M. T., Van Zandt, S. E., **Murphy, J**., & Jordan, E. T. Evaluation of a student-nurse doula program: An analysis of doula interventions and their impact on labor analgesia and cesarean delivery. *J Midwifery Womens Health*. 2012 Jan-Feb;57(1):28-34. doi: 10.1111/j.1542-2011.2011.00091.x.

* Tandon S.D., Colon L., Vega P., **Murphy J**., Alonso A. Birth outcomes associated with receipt of group prenatal care among low-income Hispanic women. *J Midwifery Womens Health*. Sep 2012;57(5):476-481.

Publications in review:

Mark, H., Roth, C., Dangerfield, D., **Murphy, J.,** & Farley, J.E. What's New in Sexually Transmitted Infections for People Living with HIV.

Abstracts:

*** Murphy, J.,** Agwu, A. Nursing Knowledge, Attitudes, and Practice Regarding Adolescent & Young Adults with HIV/AIDS. Association of Nurses in AIDS Care (ANAC) 24th Annual Conference, Baltimore, MD, November 17- 19, 2011.

***Murphy, J.,** Mark, H., Farley, J., & Anderson, J. The Self-Collection Study. Poster presented at American College of Nurse-Midwives Convention, May 29-June 2, 2013.

*** Murphy, J**. Dissertation poster presentation. Washington Regional Nursing Research Consortium (WRNRC) 3rd Annual Doctoral Student Research Conference. Accepted for presentation November 12, 2012.

EDITORIAL ACTIVITIES:

2013 – present	Peer Reviewer *Journal of the Association of Nurses in AIDS Care*
2009 – present	Peer Reviewer *Journal of Midwifery and Women's Health*
2010	Ad-hoc Peer Reviewer *Research in Nursing and Health*

PROFESSIONAL ACTIVITIES:

2012 – 2013	**PhD Curriculum Committee Representative** Doctoral Student Organization Johns Hopkins University School of Nursing
June, 2012	**Student Ambassador** Summer Research Institute on Developing Behavioral Interventions Johns Hopkins University School of Nursing
2010	**Biostatistics Tutor** PhD Program Johns Hopkins University School of Nursing.
2010 – 2011	**President** Doctoral Student Organization Johns Hopkins University School of Nursing.
2007 – 2008	**Representative to New York Medical Malpractice Task Force** New York State Association of Licensed Midwives (now known as the American College of Nurse-Midwives' New York affiliate)

PROFESSIONAL ORGANIZATIONS:

American College of Nurse-Midwives: Maryland affiliate
American Society for Colposcopy and Cervical Pathology
Association of Nurses in AIDS Care

Association of Reproductive Health Professionals
International Network for Doctoral Education in Nursing
Sigma Theta Tau, *Delta Mu* chapter
Wound, Ostomy and Continence Nursing Society

TEACHING EXPERIENCE:

2012 – 2014	**STD/HIV Prevention Training Center at Johns Hopkins** Lecturer "Genital Human Papillomavirus Infection" "Pelvic Inflammatory Disease" *STD Intensive Course*
2011 – 2014	**Johns Hopkins University School of Nursing** Teaching Assistant (2011) and Lecturer (2012 – 2014) "HIV Epidemiology, Local to Global" "Perinatal HIV" Jason Farley, PhD, MPH, ARNP, lead faculty *Diagnosis, Care and Management of Persons with HIV/AIDS*
2013	**Johns Hopkins University School of Nursing** Teaching Assistant "Human Growth and Development Through the Lifespan" Ruth Harris, PhD, ARNP, lead faculty
2013 – 2014	**Johns Hopkins University School of Nursing** Teaching Assistant Nursing Care of Older Adults Across the Continuum Elizabeth "Ibby" Tanner, PhD, MS, RN, lead faculty
November, 2012	**Johns Hopkins University School of Nursing** Instructor: Shoulder Dystocia Simulation Laura Lucas, MSN, RN, lead faculty Undergraduate Maternity Nursing course
2010	**Johns Hopkins University School of Nursing** Teaching Assistant JoAnne Flagg, DNP, CPNP, IBCLC. lead faculty *Breastfeeding: Practice and Research*
2007 – 2009	**Centering Healthcare Institute** Faculty for *CenteringPregnancy Basic* and *Advanced* CenteringPregnancy informational lectures
2008 – 2013	**Mercy College**

Lead Instructor for:
Community Health Nursing
Capstone (undergraduate and graduate)
Transcultural Nursing
Health Assessment and Promotion (undergraduate and graduate)
Pathophysiology and Clinical Reasoning for Nurses (undergraduate)
Health Policy (undergraduate)
Contemporary Concepts in Nursing (undergraduate)
Philosophical and Theoretical Foundations of Nursing (graduate)

2009 **New York University College of Nursing**
Lead Instructor for:
Primary Care of Women (Midwifery program)
Professional Issues (Midwifery program)
Maternity Nursing (Accelerated B.S. program)

COMMUNITY SERVICE:

2013 **Invited speaker, NRSA Information Session**
"**Writing your NRSA and surviving the process"**
PhD Program
John Hopkins University School of Nursing

2011 – present **Volunteer, Reproductive Health Program**
Baltimore City Department of Health

2007 – 2009 **Area Chair for Rockland/Orange (NY) Counties**
2013 – 2014 **Interviewer**
Brown University Alumni Schools Committee

February, 2010 **Member of Doctoral Student Panel**
Admissions Office
Johns Hopkins University School of Nursing

2003 – 2009 **Sunday school teacher**
Grace Episcopal Church, Nyack NY