ICCR rotation (July 22-August 4, 2008)
Final presentation
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Title:

A provider-centered intensive educational initiative to improve rates of cervical cancer screening among HIV-positive women in Cape Town, South Africa

Study purpose and rationale:

Background

In developing populations, cervical cancer is a leading cause of cancer-related death[1]. The immense burden of morbidity and mortality associated with cervical cancer in lesser-developed settings is almost an exclusive product of global differentials in the availability of screening services for easily treated precursor lesions[2,3]. 2004 WHO surveillance data reveal that cervical cancer is the most frequent cancer among South African women, including those women between 15 and 44 years of age.[4] The age-standardized mortality rate from cervical cancer is 21.0% in South Africa, while it hovers at 8.9% in the world as a whole.[4] In contrast, only one out of each 50 cancer-related deaths among American women may be attributed to this disease (less than 0.5% of all female deaths in the United States). [4] More than any other factor, this difference reflects the "remarkable triumph" of effective cytological screening programs for women in developed populations.[2]

The severity of South Africa's cervical cancer burden multiplied by this country's human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic (2005 HIV prevalence rate of 18.8% in adults 15-49 years of age). [4] Persistent infection with oncogenic strains of human papillomavirus (HPV) is a necessary, but insufficient, condition for the development of cervical cancer. It has been reported that the immunosuppression accompanying HIV infection allows for enhanced cervical infection with HPV, as well as for reactivation of previous infection with the virus.[5] Additional studies have shown a direct interaction between HIV and HPV, apart from markers of immunosuppression such as CD4+ T-cell counts. These studies suggest that local

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[1] Goldie SG, et al. Policy Analysis of Cervical Cancer Screening Strategies in Low-Resource Settings. JAMA. 2001; 285(24): 3107-15.
[2] Parkin DM. Global cancer statistics in the year 2000. The Lancet: Oncology. 2001; 2(9): 533-43.
[3] Little RF, et al. Reversible Features of Cervical Cancer in Human Immunodeficiency Virus Infection. Cancer. 2008; 112(12): 2627-30.
[4] Human Papillomavirus and Cervical Cancer: Summary Report, South Africa. WHO, 2007.
[5] Yamada R, et al. Human Papillomavirus Infection and Cervical Abnormalities in Nairobi, Kenya, an Area With a High Prevalence of Human Immunodeficiency Virus Infection. Journal of Medical Virology. 2008; 80: 847-55.

cytokine expression and HPV viral replication may be directly up-regulated by HIV itself.[6]

When seen in association with HIV infection, cervical carcinomas have been demonstrably more aggressive, refractory to standard therapies and associated with overall worse prognoses.[7] In fact, repeated observations of such phenomena led to the identification of invasive cervical cancer as an "AIDS-defining condition" by the Centers for Disease Control and Prevention (CDC), officially placing it in the company of such well-known scourges as extra-pulmonary Tuberculosis and Kaposi's sarcoma.[6] Additionally, lower-grade levels of cervical dysplasia have been designated signs of "early symptomatic HIV infection." In women living with HIV, the annual incidence of HPV-associated cervical precursor lesions is approximately five times higher than in the general population, with a three-fold risk of developing invasive cervical cancer.[8]

Rationale

In recent years, South Africa has begun a federally funded national "roll-out" of diagnostic and treatment services for HIV-infected persons. These resources allow for not only the disbursement of antiretrovirals and testing supplies, but also result in the creation of a more broadly usable health infrastructure. These newly created points of care can serve as ideal locations for the implementation of regular screening for cervical cancer among HIV-positive women at risk.[9] As the provision of HIV-related care is decentralized, cytological screening for cervical cancer via the Papanicolau (Pap) smear can become more widely-available.[9]

Additionally, with the roll-out of highly-active antiretroviral therapy (HAART), the increased survival of women with HIV will certainly translate to a greater population in need of screening for cervical cancer. Additionally, any new modalities for decreasing the morbidity and mortality of cervical cancer will rely on enhanced screening programs for disease detection. As such, this study will seek to test an intervention to increase the proportion of HIV-positive women screened for cervical cancer and its treatable precursor lesions.

Literature review:

A review of effective community-based interventions utilized for increasing rates of screening for cervical cancer in South Africa and in other sites led to the selection of a provider-directed educational intervention for increasing the proportion of women

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[6] Danso D, et al. Cervical screenig and management of cervical intraepithelial neoplasia in HIV-positive women. International Journal of STD & AIDS. 2006; 17: 579-86.
[7] Paulo M, et al. The Environmental Cofactors in Carcinogenesis in High Risk HPV/HIV-Positive Women. The Brazilian Journal of Infectious Diseases. 2007; 11(2): 189-95.
[8] Soncini, et al. Reductions of the risk of cervical intraepithelial neoplasia in HIV-infected women treated with highly active antiretroviral therapy. Acta Biomed. 2007; 78: 36-40.
[9] Franceschi S and Jaffe H. Cervical Cancer Screening of Women Living with HIV Infection: A Must in the Era of Antiretroviral Therapy. Clinical Infectious Diseases. 2007; 45: 510-3.

undergoing Pap smears. Provider-directed interventions were selected because such interventions have been shown to be more targeted and more lasting in their effects than client-directed media interventions in a South African population.[10]

More specifically, evaluations of the effectiveness of provider-directed interventions to improve rates of screening for cervical and other types of cancer reveal specifically that educational programs which positively influence provider attitudes and intentions regarding screening to be the most efficacious.[11] Even greater than provider incentives, educational programs encouraging providers to deliver screening at appropriate intervals can improve rates of cervical cancer detection.[11] A recent meta-analysis of U.S.-based provider-directed educational programs showed a median increase in rates of cervical cancer screening of 9 percent post-intervention.[11] This large analysis also showed that the absolute effect of such interventions is greatest when baseline adherence to screening is low, as is the case in South Africa. Though specific program evaluation data from international studies is limited, reviews of U.S. studies consistently show that physician-recommended Pap test are more likely to be sought out and completed.[12]

A review of existing literature also led to the decision to encourage providers to "package" health services for HIV diagnosis/care with Pap smears, as such packaging has been shown to increase health gains in health systems with both financial and personnel shortages.[13]

Hypothesis:

Null hypothesis

No difference is detected in the proportion of women newly-diagnosed with HIV being screened by Pap smear for cervical cancer/precursor lesions between control and intervention samples.

Alternative hypothesis

A difference is detected in the proportion of women newly-diagnosed with HIV being screened by Pap smear for cervical cancer/precursor lesions between control and intervention samples.

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[10] Risi L, et al. Media interventions to increase cervical screening uptake in South Africa: an evaluation study of effectiveness. *Health Education Research.* 2004; 19(4): 457-68.
[11] Sabatino SA, et al. Interventions to Increase Recommendation and Delivery of Screening for Breast, Cervical and Colorectal Cancers by Healthcare Providers. *Am J Prev Med.* 2008; 35(18): S67-74.
[12] Eaker ED, et al. "Women's Health Alliance Intervention Study: Increasing Community Breast and Cervical Cancer Screening. *J Public Health Management Practice.* 2001; 7(5): 20-30.
[13] Kim JJ, et al. Packaging Health Services When Resources Are Limited: The Example of a Cervical Cancer Screening Visit. *PLoS Medicine.* 2006; 3(110): 2031-6.

Study design:

This experimental study is designed as a randomized trial with both intervention and control arms. The study observations will be drawn from six HIV clinics in the Khayelitsha township - a poor, largely black-African peri-urban settlement surrounding the city of Cape Town. All six of these clinics were founded in the past 10 years as part of the national South African plan for roll-out of HAART and HIV/AIDS care. As such they are all very similar in their operational characteristics and staff. Their clientele differ only in geographic area within the Khayelitsha area.

Prior to clinic randomization, the six clinic sites will be grouped into pairs matched by observational data collected by chart review from each clinic site before study initiation. Clinics will be matched based on:

- Number of providers per patient encounters (preceding 12 month period)
- Average patient age (preceding 12 month period)
- Average patient income (preceding 12 month period)
- HIV infection rate at that clinic site (baseline)

Matching of clinics into three pairs will be carried out in the hopes of maintaining randomization. Once clinics have been paired, one clinic from each pair will be randomized to either the control or intervention arm of the study.

Three of the six clinics will be randomized to this study's control arm. In these three clinics, a team of three research assistants will visit these clinics once at study start date and again six months later. At both visits, researchers will provide all health providers at each clinic site (i.e., physicians, nurses, allied health professionals) and ancillary staff with standard provider-appropriate literature regarding guidelines for cervical cancer screening/Pap smears in women with and without HIV. Such literature will be disseminated at control sites in the form of flyers, and will recapitulate the most recent cervical cancer screening guidelines from the South African Ministry of Health, the World Health Organization and the CDC. Literature will be available in English, Zulu and Afrikaans.

The remaining three clinics will be randomized to the intervention group. Again, a team of three research assistants will visit these clinics once at study start date and again six months later. Each visit will be composed of an intensive, three-hour "in-service" program for all health providers that will include:

- The most recent cervical cancer screening guidelines from the South African Ministry of Health, the World Health Organization and the CDC, as above
- Information on the important link between HIV and cervical cancer
- Ways to link cervical cancer screening closely to regular HIV care, and the goal of doing so
- A discussion of common barriers to cervical cancer screening among clients, with potential solutions (i.e., better patient education, reassurance of safety of procedure, cultural concerns regarding pelvic exam)

A separate brief discussion will be held with ancillary staff at each of the two visits to reinforce the importance of immediate screening appointments for new clinic clients.

Twelve months after the study's start date, data from the clinic charts of all study subjects (see Inclusion criteria), and from clinic Pap smear registers at each of the six sites will be examined with the goal of collecting information regarding several subject characteristics (see Analyses).

Sample size:

$n_{control}$ = 160
$n_{intervention}$ = 160

Baseline proportion of all women undergoing cervical cancer screening in South Africa estimated to be 5%.[14,15]

Calculated for chi-square analysis with 2 groups; alpha = 0.05, power = 0.80. Detectable difference in proportion of women being screened for cervical cancer is 10%.
Source: http://www.biomath.info/crc/

Analyses:

Descriptive statistics

The following subject characteristics will be recorded from patient charts and clinic Pap smear registers. All data will be fully stripped of all identifiers:

- **Client participation in at least one Pap smear during the study period** (primary outcome of interest)
- Age
- Gravity and parity
- Date of HIV diagnosis
- Type of Pap abnormality, if identified (i.e., ASC-US, ASC-H, LSIL, HSIL, SCC)
- CD4+ T-cell count at time of HIV diagnosis
- Contraception use at time of HIV diagnosis (specify type of contraception utilized)
- Smoking status
- History of previous screening by Pap smear, assuming negative results (yes/no)

All of this data is already routinely recorded for a patient at her first visit for HIV counseling and testing. Demographic data aside from the primary outcome of interest will be arrayed in frequency tables to confirm successful randomization of subjects among control and intervention clinics.

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[14] Cronje HS and Beyer E. Screening for cervical cancer in an African setting. *International Journal of Gynaecology and Obstetrics.* 2007; 98(2): 168-71.
[15] Fonn S, et al. Prevalence of pre-cancerous lesions and cervical cancers in South Africa - a multicentre study. *S Afr Med J.* 2003; 93(4): 279.

Hypothesis testing

A Pearson's chi-square analysis will be carried out using the proportion of women screened during the twelve-month study period

- Control sites:

$$\frac{\text{(number of women newly diagnosed with HIV obtaining Pap smear at control clinics over study period)}}{\text{(total number of women newly diagnosed with HIV at control clinics over study period)}}$$

- Intervention sites:

$$\frac{\text{(number of women newly-diagnosed with HIV obtaining Pap smear at intervention clinics over study period)}}{\text{(total number of women newly diagnosed with HIV at intervention clinics over study period)}}$$

Alpha (Type I error) will be set at 0.05, as is customary. Power (1-beta) will be set at 80%. As described in Sample size above, effect size will be set at a minimum of a 10% increase in the proportion of women screened by Pap smear during the twelve-month study period.

Study subjects:

Inclusion criteria

This study will enroll women newly diagnosed with HIV by ELISA/rapid HIV test at one of six previously described clinic sites in Khayelitsha. Subjects will have no history of prior treatment for known cervical disease. Participants may be pregnant at the time of enrollment, and may become pregnant during the course of the study. Participants may have previous history of completed Pap smear (with no abnormalities).

Exclusion criteria

Women who are already known to be HIV-positive will be excluded from this study. History of previous abnormal Pap smear or referral to colposcopy will also be grounds for exclusion. Women with history of known prior cervical disease or vaccination against HPV will also be excluded from this study.

Recruitment

All potential study subjects (women presenting to any of the six clinic sites for HIV counseling and testing - see Inclusion criteria) will be provided information for informed consent. Information regarding the aims of the study, as well as all risks, benefits and alternatives will be provided both in writing and orally in English, Zulu and Afrikaans to all potential participants. Should a woman elect not to participate in the study, she will be informed that the quality of care she receives will not be compromised. All health

professionals and clinic staff will also provide informed consent for participation in intervention and control groups for this study. Approval will be sought from the institutional review boards of all parties involved.

Confidentiality of study data:

Women will be informed that all patient data will be de-identified and maintained in strict confidence. Confidentiality will also apply to data regarding HIV diagnosis. All patient data will be presented only in an aggregate, anonymous format. The study database will be maintained without identifiers, and will be password-protected.

Potential risks:

Immediate risks to patients and providers involved in this study will be minimal. There may be a risk of discouraging HIV testing among clients presenting to the clinic who do not wish to participate in this study.

Potential benefits:

The primary goals of this intervention will benefit both clients and providers by increasing screening for, and the earlier diagnosis of, cervical cancer among women with HIV. One also suspects that educational interventions targeting health providers will improve patient care as a whole.

Alternatives:

A "before/after" or internal control design was considered in designing this study. However, it was decided that isolating any positive effects of provider education on cervical cancer screening would be difficult without the presence of a control group. The external influences of secular trends will be easier to account for in a controlled design.

Other issues:

Study location may come into question in this trial, as it will be carried out internationally. It is most appropriate to pilot such a provider education program in a setting where it will likely be applied and achieve the greatest level of benefit. A similar argument can be made for the inclusion of study subjects traditionally identified as being part of a "special population."