

Framework in Global Health
Global Health Scholars Program

February 2009 Fellowship Recipient

Proposal Title:

“Prevalence of abnormal pap smears among HIV-positive women in Santiago, Dominican Republic”

Title: Prevalence of abnormal pap smears among HIV positive women in Santiago, Dominican Republic.

Dates of study: January and February 2010

Location: Santiago, Dominican Republic

Foreign Institution: Hospital Regional Universitario José Maria Cabral y Báez, Santiago, Dominican Republic. The collaboration between Brown University and Cabral Hospital began in 2003. The HIV program at Cabral was developed by Dr. Michael Stein in conjunction with Drs. Francisco Mejia and Claudia Rodriguez. The program has involved the hiring of staff in the Dominican Republic with Brown funding, the interchange of medical student and residents, the placement of a Brown student for year-long rotations in the clinic, and the institution of an electronic database in Santiago that serves both clinical and research functions.

Brown Faculty Mentor: Susan Cu Uvin, MD. Currently Dr. Cu Uvin supervises my clinical training at the Miriam Hospital Immunology clinic. She also provides support on local research projects related to the clinic.

Primary Aims:

1. To assess the prevalence of cervical cytological abnormalities (pap smear) among HIV positive women in Santiago.
2. To assess the persistence of abnormal cervical cytology among HIV positive women in Santiago.

Secondary Aim:

1. To collect information on risk factors (low CD4 count, high plasma viral load, antiviral therapy, number of sexual partners, use of condoms, smoking) associated with cervical HPV infection.

Background and Significance: The leading cause of cancer deaths in women in developing countries is cervical cancer. This is particularly true in locations without access to routine screening with pap smears where 83% of cervical cancers occur¹. Cervical cancer occurs in younger women, thereby making it the most common cause of years of life lost in Latin America and the Caribbean². Although the Dominican Republic initiated a population based screening program in 1993³, only about 54% of eligible women were screened⁴ in 2002 from a population of 2.98 million aged 15 and older. With an estimated 1032 incident cases of cervical cancer in the Dominican Republic (DR) each year, it is the most common cause of cancer death among women. Of those incident cases, about 562 die annually⁵.

Cervical high risk neoplasia is correlated with human papilloma virus (HPV) infection, specifically oncogenic strains such as 16 and 18. Women with HIV have higher rates of HPV coinfection and are less likely to clear the HPV. According to the US based HERS cohort, most pap smears in women with HIV are low grade but compared with HIV negative women, there is a rate ratio of 4.5 of developing an abnormal pap smear⁶. In

fact, cervical cancer is a criterion for the diagnosis of AIDS as stage C disease⁷. In a large US multicenter study of the natural history of HIV infection and related diseases to women, cervical cytology was found to be abnormal in 38.3% of HIV infected women. Risk factors for abnormal cytology included CD4 cell count, HIV RNA level, detection of HPV, and number of male sex partners within 6 months of enrollment among other issues⁸.

No data has been published on the prevalence of abnormal pap smears among women with HIV in the DR. However, the DR is one of the countries where the HIV epidemic is generalized, and unpublished data from 2007 reveals the rate of HIV positivity at the major public teaching hospital in Santiago was 2.76% from a total of 7,782 men and women tested⁹. Therefore, it is likely that there are significant rates of abnormal pap smears among women with HIV cared for at the Hospital Regional Universitario José María Cabral y Báez. The information gathered from this study will be the basis for further study of cervical cancer prevention in the Dominican Republic. Envisioned for the future are studies of HPV genotypes in HIV positive and negative women and a cost effectiveness analysis for HPV vaccination.

Methods: This is a retrospective chart review of 100 HIV positive women who have been followed since 2003 in the HIV clinic in Santiago, Dominican Republic. Cytological cervical smears are reported according to the 2001 Bethesda System Terminology¹⁰ and include: invasion, high or low grade squamous intraepithelial lesion (HSIL or LSIL), atypical glandular cells of undetermined significance (AGUS), atypical squamous cells suggesting HG (ASC-H) or atypical cells of undetermined significance (ASCUS). An abnormal pap smear is defined as any smear with pathological diagnosis of ASCUS or higher grade. The prevalence of abnormal pap smear is defined as the total number of abnormal pap smears divided by the total number of charts reviewed. Because fewer than 50 women have had more than one pap smear, it is not possible to determine incidence, defined as a normal pap smear is followed by an abnormal pap smear. However it is possible to determine persistence of abnormal pap smear since women with abnormal pap smears are followed according to national guidelines that require colposcopy for low grade squamous intraepithelial lesions (LGSIL) or higher. For this study, persistence is defined as two consecutive abnormal pap smears. One limitation of the study design is that it does not allow us to differentiate between persistence and intermittent reinfection which can also be a source of subsequent abnormal pap smears.

Data Collection Procedures: The HIV clinic's database will be queried for all women who have had a pap smear; currently there are 226. One hundred subjects will be randomly selected from the women who have a pap smear recorded in the database. Subjects with unsatisfactory pap smears or vaginal cytology will be excluded. Their paper charts will be reviewed and demographic data abstracted. In addition, information on risk factors associated with cervical HPV infection will be

collected such as CD4 count, plasma viral load, antiviral therapy, number of sexual partners, use of condoms, history of sexually transmitted infections, gravidity, and smoking. Information about the cytology and follow up will be recorded. This will be used to determine prevalence.

Regarding persistence, all the women with abnormal pap smears will be initially included. There are approximately 52 subjects with abnormal pap smears. Of those, all paper charts with follow up pap smears and/or colposcopy will be included. Any woman who has not had a follow up pap smear recorded will be eliminated from the analysis. Demographic information will be abstracted from the chart. Similarly, risk factors will be collected as above. Persistence will be calculated by the number of subjects with two sequential abnormal pap smears or colposcopies divided by the total number of women who have had abnormal pap smears.

Analysis: The association between abnormal follow-up smears and demographic and clinical predictors will be examined using logistic regression. Initially, univariate analysis will be used to determine which variables are associated with abnormal cytology. Based on statistically significant associations from the univariate analysis, multivariate logistic models will be developed. All statistical analysis is to be conducted with SAS 9.1 (SAS Institute Inc., Cary, NC)

Plan for Dissemination: The study results will be presented at a national conference such as the Infectious Disease Society of America. In addition, at least two manuscripts will be submitted to peer reviewed publications such as Lancet Infectious Disease, Journal of AIDS, or Journal of Infectious Disease.

Detailed Budget: The cost of the study is \$2910. Please see table below.

Study materials: files, folders, computer discs, database access	650
airfare, 450\$ (from expedia)	450
meals, 10\$ per day, x 8 weeks	560
research assistant, 20% time clinic nurse for accessing charts	250
Accommodations, 1000\$ for 8 weeks	1000
Total	\$2,910

References:

¹ Schiffman M, Castle PE. The promise of global cervical-cancer prevention. N Engl J Med. 2005;353:2101-2104.

² Yang BH, Bray FI, Parkin DM, Sellors JW, Zhang ZF. Cervical cancer as a priority

for prevention in different world regions: an evaluation using years of life lost. *Int J Cancer* 2004;109(3 (April)):418–24.

³ Murillo R, Almonte M, Pereira A, et al. Cervical Cancer Screening Programs in Latin America and the Caribbean. *Vaccine* 26S (2008) L37–L48.

⁴ <http://www.who.int/healthinfo/survey/whsdom-dominicanrepublic.pdf>

⁵ WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Summary report on HPV and cervical cancer statistics in Dominican Republic. 2007. [12/02/08]. Available at www.who.int/hpvcentre

⁶ P Schuman, SE Ohmit, RS Klein, et al. Longitudinal Study of Cervical Squamous Intraepithelial Lesions in Human Immunodeficiency Virus (HIV)–Seropositive and At-Risk HIV–Seronegative Women. *Journal of Infectious Diseases*, 2003; 188: 128–36.

⁷ From the Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *JAMA*. 1993 Feb 10;269(6):729–30

⁸ Massad, L, Riestler, K, Anastos, K et al. Prevalence and predictors of squamous cell abnormalities in papanicolau smears from women infected with HIV-1. *Journal of Acquired Immune Deficiency Syndromes*. 1999; 21 (1) 33–41.

⁹ Veras, B. *Prevalencia de Casos positivos de VIH en pruebas realizadas en el Hospital Jose Ma. Cabral y Baez, Santiago, Rep. Dom., 2007*. Boletín Notas de Epidemiología Vol No.5. Octubre 2008

¹⁰ Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright TJ, Young N. The 2001 Bethesda System. Terminology for reporting results of cervical cytology. *JAMA*. 2002;287:2114–2119.