Prevalence, Risk Factors and Pregnancy Outcomes of Cervical Cell Abnormalities in the Puerperium in a Hyperendemic HIV Setting

By

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AUTHOR'S DECLARATION

I, Dr Hopolang Maise, declare as follows:

1. That the work described in this dissertation has not been submitted to UKZN or any other institution for the purposes of an academic qualification, whether by myself or any other party.

2. That my contribution to the project is as follows:
    - Conceptualized the study
    - Literature review
    - Formulation of study protocol
    - Supervision of data entry
    - Final manuscript
    - Final Dissertation

3. That the contributions of others to the project are as follows:

    - Professor D Moodley
        - Assistance with study concept
        - Final editing of study protocol
        - Assistance with writing manuscript
        - Final editing of manuscript
    - Professor B Sartorius
        - Data analysis
        - Complete statistical guidance to interpreting and presenting the findings
    - Dr M Sebitloane
        - Expert advice on interpreting the data
        - Contributed to writing of final draft of the manuscript

Signed: _____Date: _____

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I thank the following regulatory bodies for permission to conduct this study

1. Biomedical Research Ethics Committee (BREC)
2. Postgraduate Research and Education
3. Dept of Health in KZN

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ACRONYMS

ANC	Antenatal Clinic
ART	Antiretroviral Treatment
ASCUS	Atypical Squamous Cell of Undetermined Significance
BREC	Bio-Medical Research and Ethics Committee
CIN	Cervical Intraepithelial Neoplasia
HPV	Human Papilloma Virus
HGSIL	High Grade Squamous Intraepithelial lesion
HIV	Human Immunodeficiency Virus
LBW	Low Birth Weight
LGSIL	Low Grade Squamous Intraepithelial Lesion
PMTCT	Prevention of Mother to Child Transmission
PHC	Primary Heath Care
PROM	Premature Rupture Of Membranes
PTD	Preterm Delivery
PTB	Preterm Birth
RCT	Randomised controlled trial
SAHAPS	South Africa HIV/AIDS Post-test Support (SAHAPS) Study
SGA	Small for Gestational Age
SIL	Squamous Intraepithelial Lesion
STIs	sexually transmitted infections

ABSTRACT

Objective

We investigated the impact of cervical cell abnormalities detected in the puerperium in association with HIV-1 infection on pregnancy outcomes.

Methods

A behavioural intervention RCT enrolled 1480 pregnant women (≥18years) at a peri-urban primary health clinic in South Africa during May 2008-June 2010. A pap smear was performed 14weeks postpartum and sent to the local laboratory services for cytology. We performed a secondary data analysis of pregnancy outcomes, Pap smear results (cytology), HIV results and participant demography.

Results

564 women (38.1%; 95%CI35.7-40.1) were HIV-1 positive and 78(8.0%; 95%CI6.4-9.9) women tested positive for cervical cell abnormalities at the postpartum visit. Forty two (4.2%; 95%CI 3.1-5.6) women presented with LGSIL, and 7 (0.7%; 95%CI 0.3-1.4) with HGSIL. In an adjusted analysis, HIV-infected women were significantly more likely to test positive for LGSIL ($p<0.001$) and HGSIL ($p=0.011$). Premature birth, low-birth weight and non-live birth rates were similar among HIV-infected and uninfected women with abnormal cervical cytology. Low-birth weight was also significantly more common among HIV infected women with normal cervical cytology.

Conclusion HIV-infected pregnant women are more likely to be diagnosed with higher grades of squamous cell abnormalities. There is no evidence of an association between squamous cell abnormalities/HIV comorbidity and adverse pregnancy outcomes.

Synopsis

HIV-infected pregnant women are likely to present with higher grades of cervical cell abnormalities in the puerperium but without any evidence of adverse pregnancy outcomes.

CHAPTER 1

INTRODUCTION

Cervical cancer is the most common malignancy discovered during pregnancy, with an incidence of 1.2-4.5 per 10,000 women (Creasman 2001, Duggan 1993). It is the leading cause of cancer death in most parts of Sub-Saharan Africa, South America and South Asia (Yang 2004). The direct precursor of cervical cancer is represented by Cervical Intraepithelial Neoplasia (CIN), that is usually detected and managed through the Papanicolaou (Pap) test cytological screening and/or high risk Human Papillomavirus (hr-HPV) DNA testing.

The incidence of abnormal cervical cytology during pregnancy is at least as high as that reported for non-pregnant women. In fact, 1-8% of pregnancies are complicated by an abnormal Papanicolaou smears (Insinga 2004).Thus, it is strongly recommended that all pregnant patients undergo cervical screening at the time of their initial prenatal visit, as pregnancy can represent a unique opportunity to approach otherwise unscreened women (Hunter 2008, ACOG 2002).

The main documented adverse effect of treated or untreated premalignant lesion in pregnancy is preterm birth (Danhof, 2015, Jakobsson 2007, He 2013). Other potential adverse outcome studied are miscarriages (Conde-Ferraez 2013), PROM (Cho 2013), stillbirth, and poly/oligohydramnios (Ticconi 2013, He 2013).

1.1 RATIONALE FOR THE STUDY

There is limited data with regards to untreated CIN, HIV and adverse pregnancy outcomes in South Africa. We seek to add to the body of available evidence.

1.2. HYPOTHESIS

Squamous intraepithelial lesions diagnosed in the puerperium is associated with adverse birth outcomes.

1.3. AIM OF THE STUDY

The overall aim of this study was to describe the prevalence of squamous intraepithelial lesions in pregnancy diagnosed in women in the puerperium and investigate associated birth outcomes.

1.5 .SPECIFIC OBJECTIVES

- To determine the prevalence of squamous cell intraepithelial lesions in the puerperium using routine pap smear screening.

- To explore an association between demographic characteristics and squamous intraepithelial lesions
- To describe clinical characteristics (Parity, contraception, CD4+ Count) in women presenting with squamous cell intraepithelial lesions in the puerperium.
- To describe potential relationships between squamous cell intraepithelial lesions and other STIs including HIV
- To compare Perinatal outcomes [Preterm birth (PTB), Low Birth weight (LBW), and Stillbirth (SB)] in women presenting with and without squamous cell intraepithelial lesions.

CHAPTER 2
LITERATURE REVIEW

2.1. Definitions

***Cervical Intraepithelial Neoplasia (CIN)*:** The direct precursor of cervical cancer is represented by Cervical Intraepithelial Neoplasia (CIN), that is usually detected and managed through the Papanicolaou (Pap) test cytological screening and/or high risk Human Papillomavirus (hr-HPV) DNA testing.

Atypical squamous cells of undetermined significance (ASC-US): ASC-US means that changes in the cervical cells have been found. Squamous cells are thin and flat and grow on the surface of a healthy cervix. In the case of ASCUS, the Pap smear reveals slightly abnormal squamous cells, but the changes don't clearly suggest that precancerous cells are present. The changes are almost always a sign of an HPV infection. ASC-US is the most common abnormal Pap test result.

Low-grade squamous intraepithelial lesion (LGSIL): LGSIL means that the cervical cells show changes that are mildly abnormal. LSIL usually is caused by an HPV infection that often goes away on its own.

***High-grade squamous intraepithelial lesion (HGSIL)*:** HGSIL suggests more serious changes in the cervix than LGSIL. It is more likely than LGSIL to be associated with precancer and cancer.

Preterm Births: Births occurring <37 weeks gestation were defined as preterm.

***Low Birth Weight*:** Low birth weight was defined as <2500g in term deliveries $\geq$37 weeks gestation.

Stillbirth: Stillbirths are defined as foetal demise $\geq$ 21 weeks gestational age.

Miscarriage: A miscarriage is defined as foetal demise <21 weeks.

2.2. **Epidemiology of Cervical Intraepithelial Neoplasia**

A total of 715 000 cases of cancer were newly diagnosed in 2008 alone in Africa. Cervical cancer was the commonest type of cancer in women in sub-Saharan Africa (31.7/100 000) (Jemal 2012). In Southern Africa, cervical cancer was the 2nd commonest type of cancer in women, second to breast cancer (26.8/100 000). Accordingly, cervical cancer was the leading cause of cancer-related deaths in women in SSA (22.5/100 000) and the second leading cause of cancer related deaths in Southern Africa (14.8/100 000). Pap test screening (organized or opportunistic) allows the detection and removal of precancerous lesions (Bray 2005, Parkin 2008, Mathew 2009, Vizcaino 2000). In several western countries, where screening programs have long been established, cervical cancer rates have decreased by as much as 65% over the past four decades. For example, in Finland, cervical cancer incidence rates decreased from 21.1 in 1966 to 7.3 in 2007 (IARC 2007).

2.3. **Risk Factors for Cervical Intraepithelial Neoplasia**

Human papillomavirus (HPV), a sexually transmitted infection, is clearly established as a necessary agent in the development of cervical cancer (La Ruche 1998, Smith 2003, Kumar 2005, Baseman 2005, Castellsague 2002, Hawes 2003, Shapiro 2003, Walboomers 1999). There is increasing evidence that HPV increases risk of HIV acquisition, ie. women who are HIV infected are more likely be infected with HPV too. Being HIV positive, women have a higher prevalence of HPV across all age groups and more particularly in the reproductive age. HPV prevalence in HIV positive women was 74% as compared to 36.7% in HIV negative women (Mbulawa 2015). Pregnancy seems to be a risk factor for cervical HPV infection or increased replication of the persisting virus due to the associated increased hormonal level or immunosuppression (Castellsague 2006). Persistent infection with about 15 high-risk human papillomavirus (HPV) types is the major risk factor for cervical cancer, with HPV-16 and HPV-18 infections accounting for about 70% of the total cases (Castellsague 2006).

Exposures related to sexual and reproductive behaviour play an important role in the aetiology of cervical cancer. Other established risk factors include smoking, increasing parity, early age at first intercourse, multiple sexual partners, and infection with other sexually transmitted diseases (Smith 2003, Kumar 2005, Baseman 2005, Castellsague 2002, Cooper 2007).

Hormonal contraceptives also seem to increase the risk of cervical cancer in most populations studied. A recent meta-analysis by the International Collaboration of Epidemiological Studies of Cervical Cancer included 24 studies conducted worldwide (Appleby 2007). It found elevated risk of cervical carcinoma associated with both oral and injectable contraceptives, increasing with

duration of use. Some studies of populations in sub-Saharan Africa, however, have not shown increased risk (Shapiro 2003, Appleby 2007).

2.4. **Natural History of Cervical Intraepithelial Neoplasia in Pregnancy**

There is no evidence to suggest that pregnancy increases the rate of CIN progression to invasive carcinoma, it occurs in 0% to 0.4% of cases; most of the intraepithelial dysplastic lesions remain stable or regress. Spontaneous regression occurs in 48% to 70% of HGSIL (High Grade Intraepithelial lesion) or CIN2-3 lesions (Yost 1999, Paraskevaidis 2002, Ahdoot 1998, Coppolillo 2013). The effect of delivery mode on regression of dysplastic lesions remains controversial (Yost 1999, Coppolillo 2013, Kaplan 2004, Brinton 1989, Kaneshiro 2005). Ahdoot et al reported a spontaneous regression in 60% of women with HSIL who had a vaginal delivery, whereas none of the patients who delivered by caesarean section showed regression (Ahdoot 1998). On the other hand, Yost et al found an overall regression of HSIL lesions in 70% of patients, irrespective of the mode of delivery (Yost 1999). It has been speculated that the cervical trauma occurring during second and third stage of labour and during delivery can lead to an inflammatory reaction in the cervix epithelium which can promote repair mechanisms. Another theory advocates the transient ischemic changes occurring to cervical tissues during ripening as responsible of lesions regressions.

2.5. **Epidemiology of HIV in Pregnancy in South Africa**

The role of HIV in the aetiology of cervical cancer is also unclear, especially in Africa. Immunosuppression is a risk factor for HPV infection and/or detection, and there is consistent evidence that HIV-positive women have higher prevalence of HPV infection, more persistent infection, and resulting higher rates of preinvasive cervical lesions (Chirenje 2005, La Ruche 1998, Baseman 2005, Castellsague 2002, Ferenczy 2003, Wright 1994, Rowhani-Rahbar 2007).

South Africa has the largest burden of HIV disease globally (UNAIDS 2014). The national antenatal HIV prevalence in 2013 was 29%, but within South Africa itself, the HIV epidemic is heterogeneous and KZN still maintains the highest antenatal HIV prevalence (40%) record over the past 2 decades (National Dept of Health, SA 2015) (Figure 1).

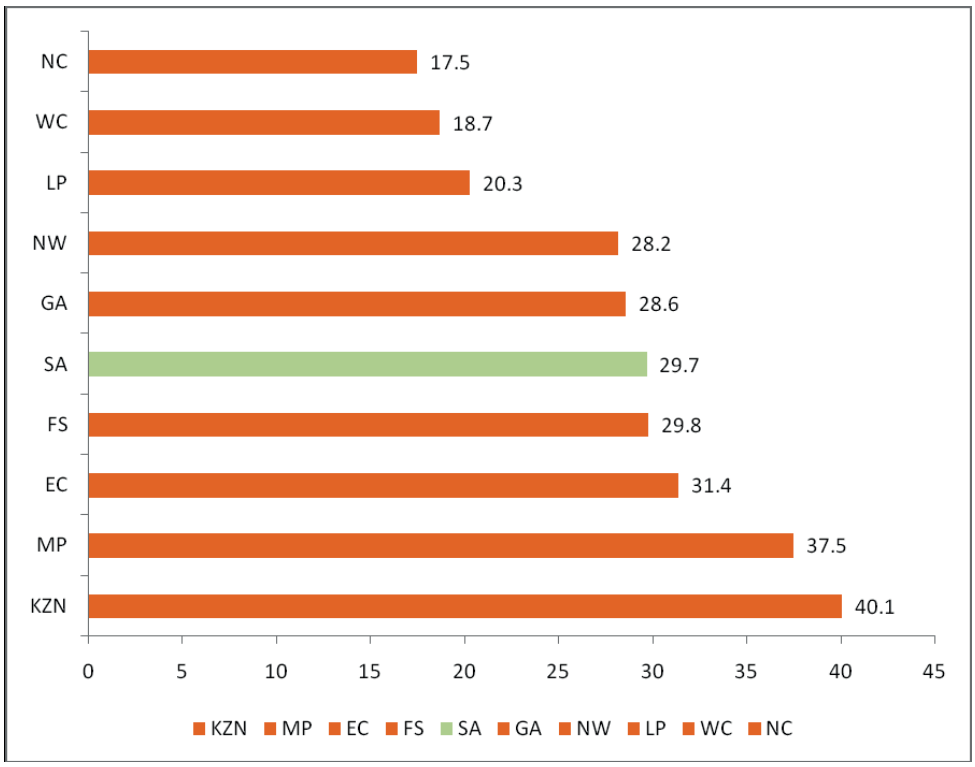

Figure 1 Provincial Antenatal HIV Prevalence in South Africa (2012)

And within KwaZulu Natal itself, the antenatal HIV prevalence ranges from 36% to 45%; with eThekwini being among the four highest burden districts (HIV prevalence >40%) (Figure 2).

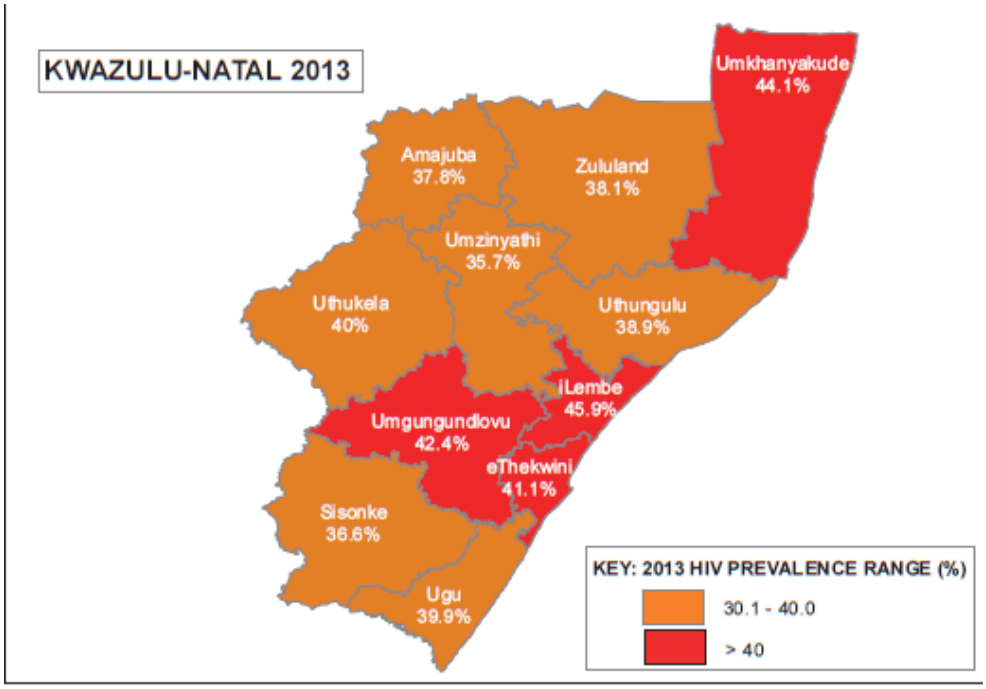

Figure 2 District Antenatal HIV Prevalence in KwaZulu Natal (2012)

South Africa has through its expansive PMTCT programme initiated more women than males on ART. The effect of this can be seen in the antenatal seroprevalence trend. The prevalence in the older age groups is reflective of established infections, with the increase in prevalence in the older age groups (>35) due to greater antiretroviral treatment access and increased survival and increased parity among women with established HIV infections (National Dept of Health, SA 2015) (Figure 3).

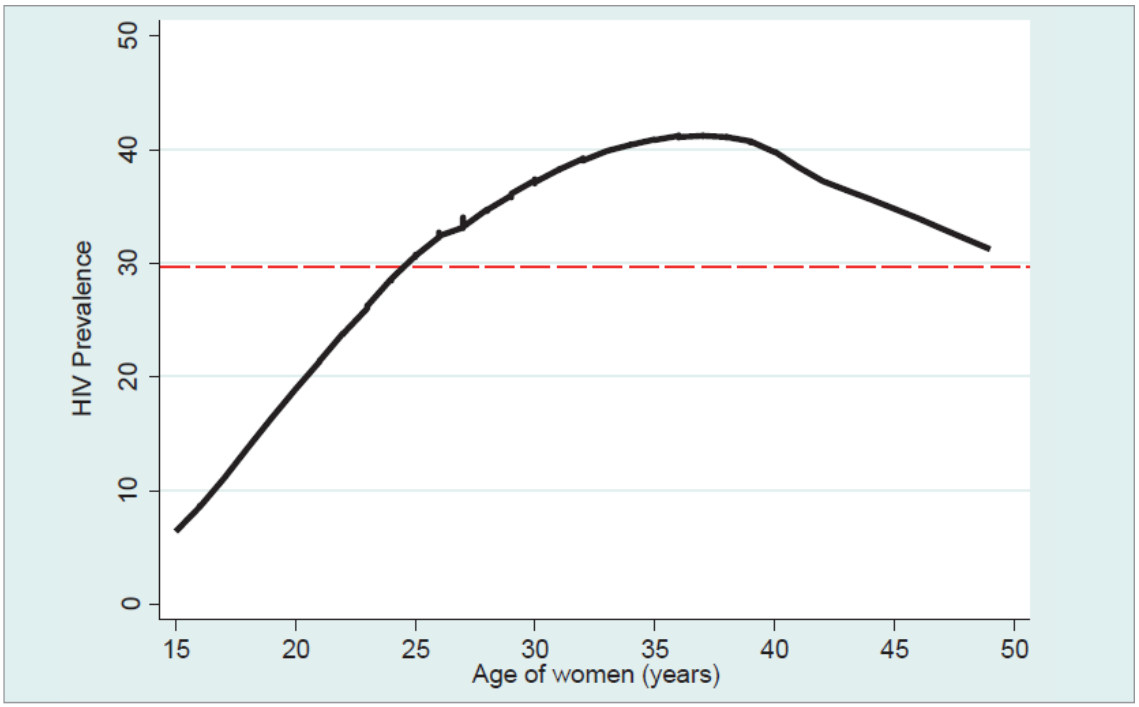

Figure 3 HIV Prevalence of Pregnant Women by Age in South Africa

2.6 Pregnancy Outcomes in South Africa

Prior to the antiretroviral rollout in South Africa, the 2003-2005 Saving Babies Report included data for 576,065 births in public health institutions in South Africa each year (MRC Research Unit for Maternal and Infant Health Care Strategies, 2007). The perinatal mortality rate was reported as 37.5 cases per 1000 births. The stillbirth, early neonatal death and low birth weight rates were 24.3, 12.2 and 15.5 cases per 1000 births respectively.

Since the antiretroviral rollout, the 2010-2011 Saving Babies Report included data for 1,324,320 births ((MRC Research Unit for Maternal and Infant Health Care Strategies, 2013). The cumulative perinatal mortality rate was reported as 25.6 per 1000 births, a significant drop in perinatal deaths since the pre-ARV Report. Similarly, the stillbirth and early neonatal death were significantly lower than that reported in the pre-ARV period (stillbirth 18.5 cases per 1000 births

and early neonatal deaths 7.2 cases per 1000 births). However, there was no significant reduction in the low birth weight rate (14.2 cases per 1000 births).

Neither of these reports attributed the adverse birth outcomes to HIV. Only recently, in a hospital audit of 10372 deliveries, Moodley et al reported 301 (2.9%) still births, 2241 (21.8%) preterm deliveries , 469 (4.6%) very preterm delivery , 1458 (14.1%) low birth weight , 349 (3.4%) very low birth weight and 870 (8.5%) were small for a given gestational age based on their birth weight being below the 10th percentile (Moodley 2016). In this analysis, unregistered pregnancies and HIV infection remained significant risk factors for still birth (OR 6.84 and 1.34 respectively), preterm deliveries (OR 1.30 and 4.44 respectively), low birth weight (OR 1.33 and 4.25 respectively) and small for gestational age (OR 1.2 and 2.31 respectively). The authors concluded that, when compared to HIV uninfected women, HIV infected women had a higher risk for stillbirth, PTD, SGA, and LBW babies. In addition, the audit confirmed that ART exposure as ZDV prophylaxis or triple ARV regimen was associated with a decreased odds of risk for an adverse birth outcome.

CHAPTER 3
METHODOLOGY

3.1 Study setting

The Umlazi Section D clinic is a primary health care (PHC) centre in Durban and is situated 17 Km Southwest of Durban. The population of it is estimated at 900 000 although some estimates indicate a higher population figure – up to 1.6 million people. There are informal shack settlements in and the surrounding areas. It is a community that amplifies South Africa's already-significant HIV rate. Most women are seen at the Umlazi Section D Clinic for all antenatal clinic visits, and then they deliver their babies at the Prince Mshiyeni Memorial Hospital. All post-natal visits and well-baby visits are conducted at the Section D clinic. The PHC clinic has an active PMTCT program. Most women start their ANC visits at 14-28-weeks gestation, and women are usually offered HIV testing at their first visit. Women are given standard HIV post-test counselling according to WHO/CDC guidelines in the form of group counselling with 8-10 other women from the ANC clinic. Those who agree to be tested are tested using rapid testing technologies. All women are given standard HIV post-test counselling.

3.2. Study Design

This dissertation is based on a secondary analysis of data collected during a randomized controlled intervention study, the South African HIV Antenatal and Postnatal Support (SAHAPS) study (Maman 2014). The SAHAPS study was a collaborative study between the University of KwaZulu-Natal and the University of North Carolina at Chapel Hill and was designed to examine the efficacy of enhanced HIV counselling and support for pregnant women in reducing sexual behaviour risk during pregnancy and postpartum. The primary outcome measures were STI incidence (Trichomonas vaginalis, Neisseria gonorrhoea and Chlamydia), consistent and correct condom use, and partner uptake of HIV VCT. The parent study was sponsored by the National Institute for Health and Child Development (NICHD), 1-R01-HD050134001-A1.

3.3. Regulatory Approvals

The parent study was approved by the Institutional Review Boards of the University of KwaZulu-Natal and the University of North Carolina at Chapel Hill. A written informed consent was obtained from all women who participated in the main study. For the secondary analysis a separate submission to the University of KwaZulu Natal IRB was approved (IRB# BE 476/15).

3.4 Study Population

There are about 9,000 first visit antenatal attendees per year at Umlazi SED Clinic. Women range in age between 16 and 40 years. Approximately 25% are primigravid and the average gestational age at first visit is 24 weeks. Pregnant women who presented to the Umlazi Section D clinic for antenatal care were screened for participation in the parent study (South African HIV Antenatal and Postnatal Study – SAHAPS study) (Maman 2014).

3.4.1 Inclusion Criteria:

- at least 18 years old
- had never tested for HIV or had tested negative for HIV at least 3 months prior to recruitment
- planned to live in Durban for at least the next year
- planned to bring their infant to the clinic for immunization visits

3.4.2 Exclusion Criteria:

- not willing to participate in the study
- we're not able to communicate in English or isiZulu
- did not have a primary intimate partner for atleast the past 6 months
- had a pregnancy complication that needed referral to a higher level of care

3.5 Sample Size

The main study was powered to allow for all statistical analyses to be stratified by HIV-status because the content of the enhanced counseling intervention differed for these two groups. Based on a 9% difference in incidence rate of STIs among HIV-positive women in the intervention and control arms and an 8% difference among HIV-negative women, 279 HIV-positive and 295 HIV-negative participants per group were needed for 80% power. For consistent condom use, this sample size has the power to detect a difference between groups of 12% for HIV-positive women and 11% for HIV-negative women.

3.6 Participant Flow in the SAHAPS Study (Parent Study)

Between May 2008 and June 2010, first visit antenatal attendees, who were eligible and consented to participate in the SAHAPS study had a baseline survey (demographics and sexual behaviour) administered, were tested for HIV, randomized to the control or intervention arm and screened for other STIs (N. Gonorrhoea, C. trachomatis, and T.vaginalis). Women received the standard antenatal care throughout pregnancy and the standard HIV PMTCT/Treatment care according to the South African guidelines for that period. At 6 and 10 week postpartum visits we conducted a medical chart review of obstetric outcomes, and provided intervention counselling sessions to women randomized to the intervention arm (Figure 4). At the 14 week postpartum visit we conducted a behavioural survey, performed a pap smear and repeated the STI screening. At 9 months postdelivery, a post-intervention survey was conducted and participants exited the study.

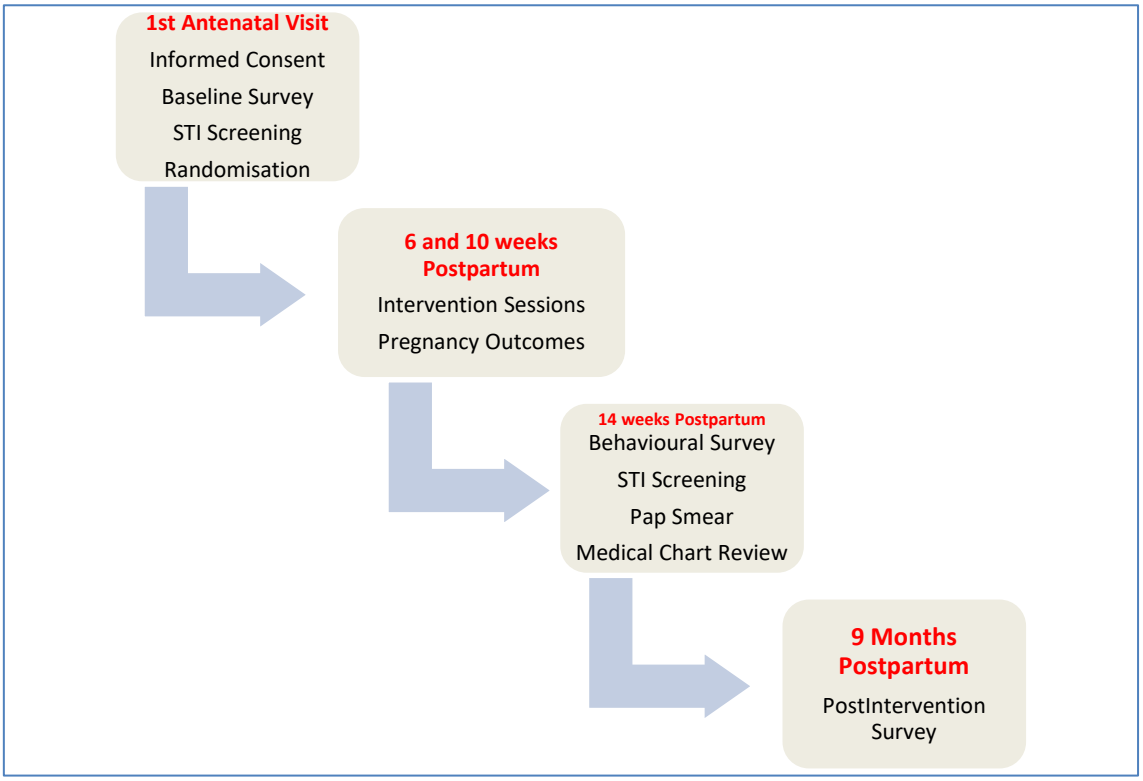

Figure 4: Participant Flow and Key Procedures in the SAHAPS Study (Parent Study)

3.7 Data Collection

For the SAHAPS study (parent study) a medical extraction form (Appendix 7) was developed to include participant demographics, pregnancy outcomes, STI results, PAP Smear Results, and HIV Status. The study nurses examined the maternity chart and infant's road-to-health card to obtain

pregnancy outcomes. The study nurses performed HIV testing, and maintained their own record of participant's HIV status, in addition to documenting the status in the maternity chart. Formal laboratory results were obtained for STIs and Pap smear, these results were transcribed onto the medical extraction forms (Appendix 7). Data capturers entered data from the medical extract forms onto a specifically designed database on ACCESS.

3.8 Statistical Analysis

Data for 1480 participants were captured in a database in real time and for the purpose of this secondary analysis select variables were imported into an Excel Spreadsheet. The variables included demographic characteristics, HIV status, obstetric history and characteristics, birth outcomes, cervical cytological results for Pap smear screening and laboratory STI investigations.

List of Categorised Variables Extracted from Main Database

Age
<20
20-25
26-35
>35
Education
No formal School
Primary
Secondary
Previous Pregnancies
0
1.-2
≥3
Chlamydia
Neiserria
Trichomonas
Negative
Inconclusive
ASC-US
LGSIL (CIN1/HPV)
HGSIL (CIN2/3)
Birth Outcomes

Live Births
Still Births
Birth Weight
<2500g
≥2500g
<1500g
Gestational Age at Delivery
<37w
≥37w
<34w
HIV Clinical Stage
Stage 1
Stage 2
Stage 3/4

Data were analysed using Stata 13.0 SE (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Ninety five (95) % confidence intervals were constructed around prevalence point estimates i.e. prevalence of CIN in puerperium. Assessment of association between continuous demographic and clinical characteristics by CIN status was assessed using the standard t-test or non-parametric Wilcoxon rank-sum test if the normality assumption is not upheld for the latter. Correlation between continuous variables was assessed using the Pearson correlation coefficient or Spearman rank correlation coefficient. Differences in frequencies of categorical demographic or clinical characteristics by CIN status and association with perinatal outcomes were assessed using the Pearson chi-square (χ^2) test or Fisher's exact test if an expected cell count contains fewer than 5 observations. Multivariable logistics regression was employed to assess factors associated with CIN after controlling for the confounding influence of other covariates. Model fit and validity were confirmed. An adjusted p-value of <0.05 was deemed statistically significant.

CHAPTER 4
RESULTS

4.1 Squamous Intraepithelial Lesions in the Study Population

Of the 1480 pregnant women enrolled in the SAHAPs study, 564 (38.1%; 95%CI 35.7-40.1) women tested HIV positive at their first antenatal visit. Pap smear results were not available for 471 (31.8%) women in this cohort. Among the 1009 women who had a Pap smear result in the postpartum period, categorization was not possible for 36 (3.6%) and 895 (88.7%) women had normal smears. The HIV prevalence (31.4% vs 32.5%; p=0.720), age distribution (50.0% vs 52.0% <25; p=0.468), non-live births (3.8% % vs 3.8%; p=1.000), preterm births (18.9% vs 18.8%; p=0.942) and LBW (4.2% vs 2.9%; p=0.205) were comparable between women who had a Pap smear result and those who did not. Of the 1009 women with a Pap smear result at the postpartum visit, 78 (8.0%; 95%CI 6.4-9.9) women tested positive for squamous cell abnormalities. Abnormalities included 29 atypical (ASC-US) cases (2.9%; 95%CI 2.0-4.1), 42 (4.2%; 95%CI 3.1-5.6) cases of LGSIL or HPV infection, and 7 (0.7%; 95%CI 0.3-1.4) cases of HGSIL (Figure 5).

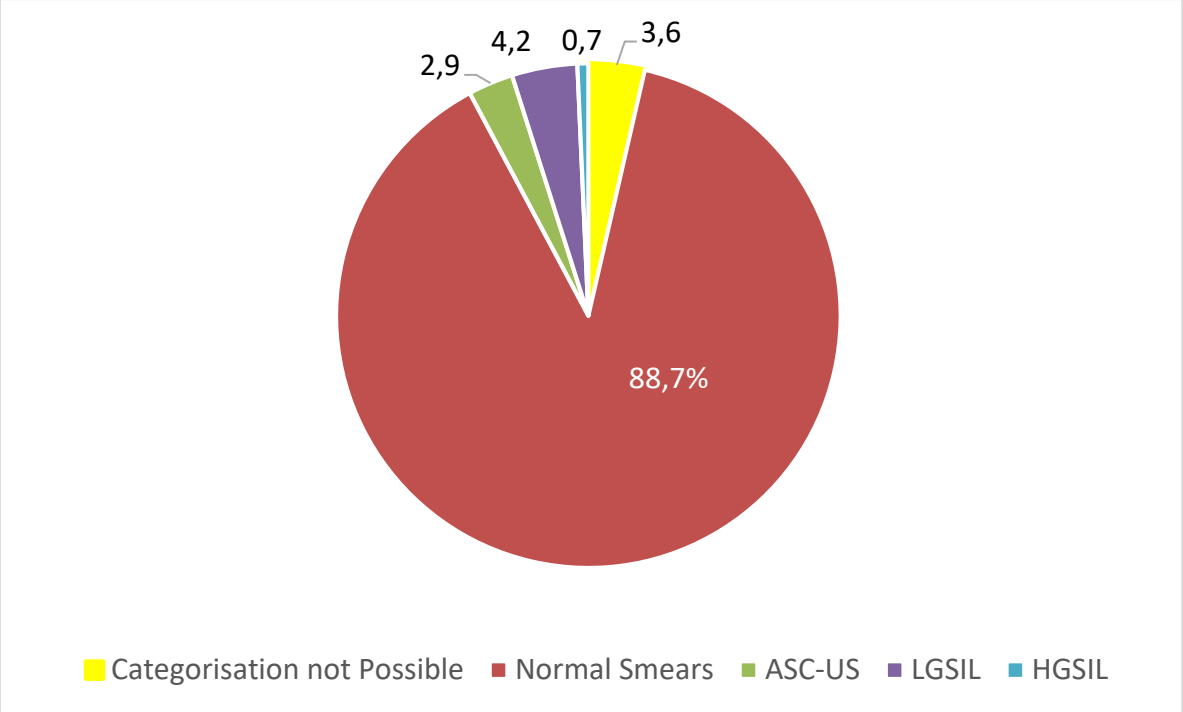

Figure 5 Distribution of Pap smear Results for Women in the Puerperium (n=1009)

The mean age of women presenting with some form of squamous cell abnormality was 24.9 years (±4.9), which did not differ significantly from women with no abnormalities (25.7 ± 5.4 years).

Younger women (≤24years) had a higher prevalence of LGSIL (4.8% vs 3.5%) while the older women (>24) had a higher prevalence of HGSIL (1.2% vs 0.2%) (p=0.550) (Table I).

4.2 Squamous Intraepithelial Lesions and HIV

After adjusting for age group, education, socio-economic status and other STIs in the multivariable analysis, women with HIV infection were significantly more likely to test positive for LGSIL or HGSIL (Table I). 34 of the 1009 (3.4%) women with a Pap smear result were HIV positive and also tested positive for squamous cell abnormalities. When compared to HIV uninfected women postpartum, the prevalence of LGSIL and HGSIL were three (7.6% vs 2.3%) and eightfold higher (1.6% vs 0.2%) among HIV-infected women respectively (p<0.0.001) (Figure 1). HGSIL was also significantly more common among women who had more than 1 pregnancy (p=0.023) (Table I).

4.3 Squamous Intraepithelial Lesions and Pregnancy Outcome

Pregnancy outcome data were available for 829 (82.2%) women with a Pap smear result. There were 8 miscarriages (1.09%; 95%CI 0.57-2.06); 17 stillbirths (2.18%: 95%CI 1.38-3.42) and 4 neonatal deaths (0.48%; 95%CI 0.19-1.24). Among the 800 live births, 91 were born prematurely (17.19%; 14.72-19.98) and 27 newborns were of low-birth weight (3.96%; 95%CI 2.69-5.77). There were no birth weight and preterm data for 57 (7.1%) and 14 (1.7%) newborns respectively. When comparing birth outcomes among HIV infected to HIV uninfected women, the proportion of livebirths (96.33% vs 96.16%; p=0.558), low birth weight (5.14% vs 3.14%; p=0.103) and preterm births (18.52% vs 19.0%; p=0.448) were not significantly different.

Table I: Characteristics of Women with and without squamous cell abnormalities in the Puerperium

	ASC-US (n=29)	Diagnosis Deferred (n=36)	HGSIL (n=7)	LGSIL (CIN1/HPV) (n=42)	Normal (n=895)	Unadjusted P value	Adjusted P value
Age group							
<24	18 (3.6)	22 (4.4)	1 (0.2)	24 (4.8)	436 (87.0)	0.072	0.548
≥24	11 (2.2)	14 (2.8)	6 (1.2)	18 (3.5)	459 (90.4)		
Education							
No Formal School	3 (5.1)	1 (1.7)	0 (0.0)	1 (1.7)	54 (91.5)	0.405	0.749
Primary	9 (2.2)	13 (3.2)	5 (1.2)	18 (4.4)	368 (89.1)		
Secondary	17 (3.2)	22 (4.1)	2 (0.4)	23 (4.3)	472 (88.1)		
Socieconomic Status							
Low	11 (2.9)	15 (3.9)	2 (0.5)	16 (4.2)	338 (88.5)	0.709	0.503
Moderate	12 (3.1)	13 (3.4)	3 (0.8)	19 (4.9)	339 (87.8)		
High	5 (2.3)	8 (3.7)	2 (0.9)	6 (2.8)	197 (90.1)		
Previous Pregnancies							
0	17 (4.7)	1 (0.3)	1 (0.3)	17 (4.7)	310 (85.9)	0.035*	0.023*
1-2	6 (1.6)	4 (1.1)	4 (1.1)	19 (5.1)	329 (88.2)		
≥3	6 (2.2)	2 (0.7)	2 (0.7)	6 (2.2)	256 (93.1)		
HIV Status							
Negative	18 (2.9)	25 (3.9)	1 (0.2)	14 (2.2)	570 (90.8)	<0.001*	<0.001*
Positive	11 (2.9)	11 (2.9)	6 (1.6)	28 (7.4)	325 (85.3)		
N.gonorrhoeae							
Negative	28 (3.0)	32 (3.4)	6 (0.6)	39 (4.1)	836 (88.8)	0.766	0.714
Positive	1 (1.8)	4 (7.1)	1 (1.8)	2 (3.6)	48 ((85.7)		
C.trachomatis							
Negative	25 (3.1)	30 (3.7)	6 (0.7)	34 (4.2)	723 (88.4)	>0.99	0.412
Positive	4 (2.2)	6 (3.3)	1 (0.6)	8 (4.4)	161 (89.4)		

In a separate bivariate analysis (Table II), birth outcomes were compared between women with and without cytological abnormalities. Similarly no marked differences in the prevalence of low birth weight babies and non-live births in these comparator groups of women was identified (Table II). Although the proportion of preterm births was higher among women with HGSIL (3 of 7; 42.9%) as compared to women with LGSIL (7 of 39; 17.9%), ASC-US (4 of 29; 13.8%) or Normal Cytology (152 of 812; 18.7%), this association was not statistically significant (p=0.222).

Table II: Pregnancy Outcomes in Women with and without squamous cell abnormalities in the Puerperium

	ASC-US (n=29)	**HGSIL (n=7)**	**LGSIL (n=39)**	**Normal (n=812)**	**Unadjusted P value**	**Total N**
Birth Outcomes (n=829)	**n (%)**	**n (%)**	**n (%)**	**n (%)**		
Miscarriage	0 (0.0)	0 (0.0)	1 (12.5)	7 (87.5)	0.938	8
Stillbirth	1 (5.9)	0 (0.0)	0 (0.0)	16 (94.1)		17
Livebirth	25 (3.1)	7 (0.9)	34 (4.3)	734 (91.8)		800
Birth Weight (n=743)						
<2500g	3 (5.2)	2 (3.4)	0 (0.0)	53 (91.4)	0.094	58
≥2500g	21 (3.1)	5 (0.7)	31 (4.5)	628 (91.7)		685
Gestational Age at Delivery (n=786)						
Preterm <37weeks	3 (5.0)	2 (3.3)	2 (3.3)	53 (88.4)	0.222	60
Term ≥ 37weeks	22 (3.0)	5 (0.7)	31 (4.3)	668 (92.0)		726

4.3 HIV-1 Infection, Squamous Intraepithelial Lesions and Pregnancy Outcomes

In comparing pregnancy outcomes among HIV infected and uninfected women with a cytological abnormality, premature birth rates, low birth weight and live birth rates were similar across all groups (Table III). Low birth weight frequency however was significantly higher among HIV positive women with normal cytological results when compared to their HIV negative counterparts (6.9% vs 3.1%; p =0.032).

Table III: Pregnancy Outcomes in Women with and without squamous cell abnormalities and/ or HIV Infection in the Puerperium

	ASC-US (n=29		**HGSIL (n=7)**		**LGSIL (n=42)**		**Normal Pap Smear (n=895)**	
HIV Status	**Pos (n=11)**	**Neg (n=18)**	**Pos (n=6)**	**Neg (n=1)**	**Pos (n=28)**	**Neg (n=14)**	**Pos (n=325)**	**Neg (n=570)**
Birth Outcomes								
Non-Live Births n (%)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	11 (4.2)	12 (2.6)
Live Birth	11	14	6	1	22	12	267	467
p value	0.345		-		0.371		0.183	
Birth Weight								
<2500g n (%)	2 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	29 (6.9)	31 (3.1)
≥2500g	8	14	5	0	20	11	222	418
p value	0.345		0.285		-		**0.026***	
Gestational Age at Delivery								
Preterm 37weeks n (%)	2 (27.3)	1 (7.1)	1 (33.3)	1 (100)	4 (19.0)	1 (0.0)	31 (15.9)	50 (17.9)
Term ≥ 37weeks	9	17	5	0	22	12	265	468
p value	0.316		0.285		0.185		0.396	

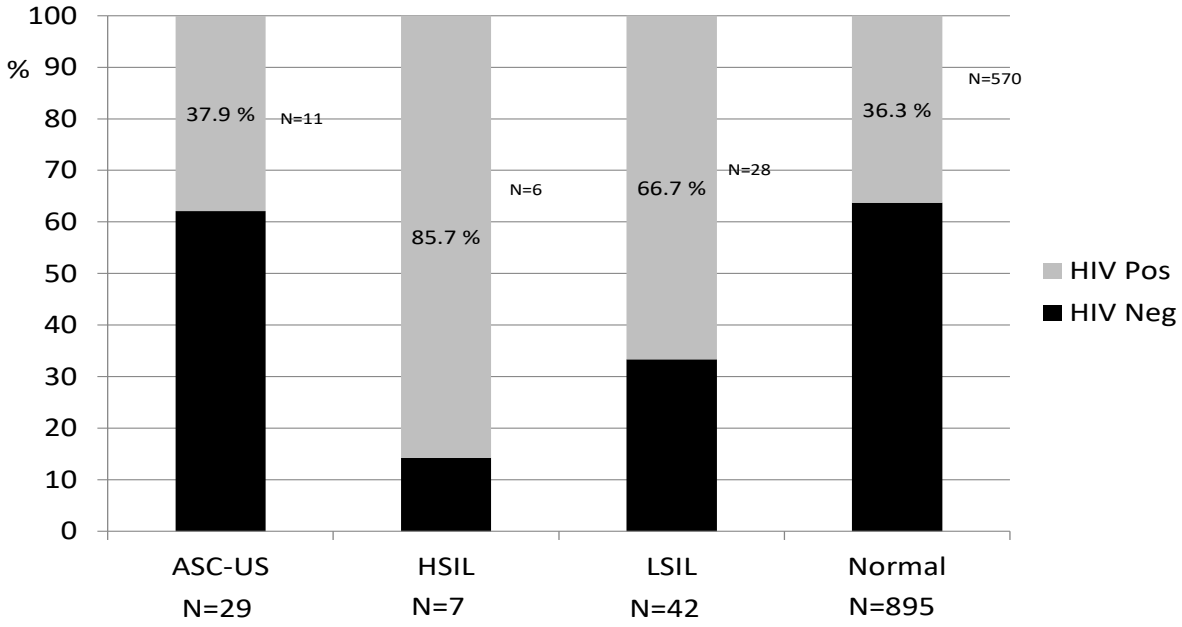

Figure 6: Proportion of HIV positive women in each category of Squamous Cell Abnormalities and Women with a normal pap smear

CHAPTER 5
DISCUSSION

A Pap smear routinely performed approximately 3 months postpartum revealed cervical squamous cell abnormalities in 8% of the study population. This is consistent with reported incidence in pregnancy of 1-8% (Insinga 2004, Palle 2000, Campion 1993, Baseman 2005). Variance in rate is related to diagnostic methods used, viz colposcopy directed biopsy confirmed versus Pap smear only. CIN lesions are secondary to persistent oncogenic HPV infection (Schlecht 2001). The sensitivity of Pap smear for SIL is 70-80% (Sherman 1998). The role of colposcopy diagnosis in pregnancy is to exclude micro invasive disease. Once micro invasive disease has been excluded, patients are managed expectantly until puerperium (Yost 1999, Vlahos 2002, Paraskevaidis 2002, Massad 2013). Persistence of SIL into the puerperium is reported to be in the region of 40-60% with regression rate of 48-70% (Yost 1999, Paraskevaidis 2002, Ahdoot 1998, Coppolillo 2013).

The timing of screening in pregnant women could be another potential reason for varying prevalence rates. Some studies presented findings from screening in pregnancy, while other studies including our study have presented findings from screening in the postpartum period (Kaplan 2004). However, there is evidence that non-invasive CIN diagnosed in pregnancy have a higher tendency not to progress during pregnancy and there is a high likelihood of these cases even regressing to a complete remission after delivery (48-70%) (Paraskevaidis 2002, Yost 1999). Only high grade CIN is more likely to persist postpartum and our prevalence of HSIL in the postpartum women (0.7%) is higher than most other reported studies of pregnant women (0.4%) (Kaplan 2004). A large population based study in Brazil also confirmed that HSIL prevalence (0.4%) in pregnant women was similar to their non-pregnant counterparts (Meyrelles 2013).

Of significance, older women with more than one pregnancy were more likely be diagnosed with HGSIL while younger women were more likely to present with atypical squamous cell appearance and LGSIL. Higher parity (≥ 3) was inversely associated with squamus cell abnormalities. This is in contrast to other studies that have found an increased rate of CIN/cervical cancer with increasing parity (Hildesheim 2001, Munoz 2002). However other studies found that parity had a borderline or no association with CIN/cervical cancer (Deacon 2000, Kruger-Kjaer 1998, Bhatla 2013). The plausible mechanism for high parity and increased risk of CIN, is postulated to be due to increased oestrogen in pregnancy leading to increased exposure of transformation zone to HPV and other cofactors over a prolonged period of time. Furthermore immune modulation in

pregnancy may promote persistence and progression of cervical dysplasia (Munoz 2002, Mathew 2009, Vizcaino 2000).

There are few studies that investigated the association between CIN and HIV in pregnancy, but most studies did not compare their findings to a HIV uninfected group of pregnant women (Meyrelles 2013, Mayaud 2001). In our study HIV infection was associated with a 3-fold increase in LSIL and eight-fold increase in HSIL in postpartum women. This association between HIV and cytological abnormalities is consistent with findings from two other South African studies of non-pregnant women and this could mainly be related to an increased persistence of high risk HPV infections in HIV-infected women (Wang 2011).This is consistent with findings by Firnhaber et al as well as Denny et al (Denny 2008, Firnhaber 2009) which is mainly related to increased persistence of high risk HPV infections in HIV-infected women (Sun 1997). In addition, HIV infected women may be set by local cervical immunological dysfunction increasing their likelihood of acquiring HPV infection (Wang 2011).

The underlying pathogenesis of HPV infection has been associated with preterm births (Al-Halal 2013, Mosbah 2017). Few studies have reported higher rates (10.7-12.2%) of preterm deliveries in untreated women with CIN (Sadler 2004, Spitzer 1995). A large study by Bruinsma et.al in 2007 which included a comparison with the general population showed an increase rate of preterm deliveries (Bruinsma 2007). A recent study published in 2013 from Beijing, also showed increased in PTB rate, as well as an increase in caesarean section and oligohydramnios in untreated women with CIN (Yue 2013).These findings suggest that characteristics of the woman or underlying pathological changes may render the woman with CIN susceptible to preterm delivery (Bruinsma 2007).

There was no association between SIL and age, educational status, which is concordant with finding by another study (Ellen 1991).

There was no association between SIL and STIs in this study. This is not surprising given the conflicting evidence of this association in the various publication. Some studies have reported a strong association especially with Chlamydia (Madeleine 2006, Smith 2004, Gopalkrishna 2000, Lehmann 1999) whilst others reported no association with any STIs (de Paula 2007, Castle 2003).

Generally, infections and associated morbidity in pregnancy are likely to alter pregnancy outcomes. Yet, there was no evidence of greater adverse pregnancy outcomes among HIV infected women with cervical cell abnormalities in our South African study cohort. Only a handful of studies have reported pregnancy outcomes for a population with cervical cell abnormalities, and none of these explored the outcomes in HIV co-infected pregnant women. Findings from these limited studies were suggestive of an association between preterm deliveries and CIN/HPV.

Our study findings appear reassuring and suggest that HIV and LGSIL or HGSIL do not alter pregnancy outcomes. We have previously shown that untreated sexually transmitted infections in pregnancy are more likely associated with adverse pregnancy outcomes (Moodley 2017).

CHAPTER 6: CONCLUSION

In conclusion, we confirm that HIV-infected postpartum women are more likely to be diagnosed with higher grades of cervical cell abnormalities. We further confirm that cervical cell abnormalities are not associated with adverse pregnancy outcomes.

6.1 RECOMMENDATIONS

Pap smears screening may be deferred to the postpartum period given the low prevalence of HGSIL at the postpartum visit and lack of association between birth outcomes and HGSIL/HIV comorbidity. There is also a need for additional studies to review the impact of the recent HPV vaccination programme in South Africa.

6.2 LIMITATIONS

There are several limitations in our study as a result of a retrospective data analysis. This included missing pregnancy outcome data, Pap smear results were not available for a large proportion of the study population and the lack of quality control measures in the performance of Pap smears.

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APPENDICES

Appendix 1: Expedited ethics approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

19 January 2016

Dr HC Maise (823826076)
Department of Obstetrics and Gynaecology
School of Clinical Medicine
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Dear Dr Maise

Protocol: Cervical intraepithelial neoplasia (CIN) in the puerperium.
Degree: MMedSc
BREC reference number: BE476/15

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 16 November 2015.

The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from **19 January 2016.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be RATIFIED by a full Committee at its meeting taking place on **09 February 2016.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: mnedlewd1@ukzn.ac.za
cc postgrad: molemong@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 3438 Facsimile: +27 (0) 31 260 4609 Email: brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

1910 - 2010
100 YEARS OF ACADEMIC EXCELLENCE

Founding Campuses: Edgewood, Howard College, Medical School, Pietermaritzburg, Westville

Appendix 2: Postgraduate approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

05 November 2015

Prof D Moodley
Department of Obstetrics and Gynaecology
School of Clinical Medicine
College of Health Science

Dear Prof D Moodley

MMedSc: "Cervical intraepithelial neoplasia (CIN) in the puerperium"
Student: HC Maise student number: 823826076

I am pleased to inform you that the abovementioned study has been approved for submission to BREC.

Please note:

- The Academic Leader: Research must review any changes made to this study
- The study may not begin without approval of the Research Ethics Committee
- A copy of the full ethics approval letter should be forwarded to the Postgraduate Office.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Miss AL Malemong
Postgraduate Administrative officer
School of Clinical Medicine

Cc Dr HC Maise Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
Postal Address: P/Bag X3, Congella, Durban, 4013, South Africa
Telephone: +27 (0) 31 260 4745 **Facsimile:** +27 (0) 31 260 4723 **Email:** malemong@ukzn.ac.za **Website:** www.ukzn.ac.za

Appendix 3: Institutional approval (SAHAPS)

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

Once the document has been signed it should be returned to Ms C Borresen, Medical Research Administration, Room 115 Old MRC Building.

To: District Manager and Area Manager: **Ethekwini District**

RE: Efficacy of HIV Post-test Support for Antenatal Care Attendees in South Africa (SAHAPS) D Moodley, Obstetrics and Gynaecology – Ref: E129/06

Permission is requested to conduct the above research study at the clinic indicated below:

Site 1 address:
Section D Clinic, Umlazi

Investigator/s:
D Moodley, S Maman,
H Sebitloane, A Kagee

Signature of District Manager :
_____

Date: _____

Signature of Area Manager:

Date: 11/7/07

DEPARTMENT OF HEALTH
ETHEKWINI DISTRICT OFFICE
12 JUL 2007
DISTRICT MANAGER
P/BAG X54378 DURBAN 4000

Appendix 4: Ethics Approval (SAHAPS)

UNIVERSITY OF
KWAZULU-NATAL

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office
Room N40 - Govan Mbeki Building
University Road, WESTVILLE CAMPUS
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: buccas@ukzn.ac.za - Website: www.ukzn.ac.za

17 July 2007

Professor D Moodley
Obstetrics and Gynaecology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Professor Moodley

PROTOCOL: Efficacy of HIV Post-test Support for Antenatal Clinic Attendees in South Africa. Prof. D Moodley, O & G. Ref: E129/06

The Biomedical Research Ethics Committee considered the abovementioned application and the protocol was approved at its meeting held on 07 November 2006 pending appropriate responses to queries raised. Your responses received 13 July 2007 to queries raised on 02 July 2007 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as at 17 July 2007. We acknowledge receipt of the permission from the Umlazi D section Clinic Manager. We also note that the study will not be undertaken at the Prince Mshiyeni Memorial Hospital.

This approval is valid for one year from 17 July 2007. To ensure continuous approval, an application for recertification should be submitted a couple of months before the expiry date. In addition, when consent is a requirement, the consent process will need to be repeated annually.

I take this opportunity to wish you everything of the best with your study. Please send the Biomedical Research Ethics Committee a copy of your report once completed.

Yours sincerely

DR J MOODLEY
Chair: Biomedical Research Ethics Committee

Appendix 5: Participant Consent (SAHAPS)

University of North Carolina-Chapel Hill
Nelson R Mandela School of Medicine, University of KwaZulu Natal
Consent to Participate in a Research Study
Adult Women from the Umlazi Section D Clinic
Enrollment and Baseline Assessment
Social Behavioral Form

IRB Study # 07-1070
Consent Form Version Date: May 03 2010

Title of Study: Intervention Phase of Efficacy of HIV Post-test Support for ANC in South Africa

Principal Investigator: Suzanne Maman, PhD, MHS
UNC-Chapel Hill Department: Health Behavior and Health Education
UNC-Chapel Hill Phone number: 919-966-3901
Email Address: smaman@unc.edu
Co-Investigators:
Dr. Dhayendre Moodley (South Africa)
Dr. Hoosen Coovadia (South Africa)
Dr. Hanah Sebitloane (South Africa)
Dr. Ashraf Kagee (South Africa)
Dr. Prashini Moodley (South Africa)
Dr. Michael Sweat (MUSC)
Dr. Shrikant Bangdiwala (UNC)
Ms. Allison Groves (UNC)
Ms. Petrica Rouse (UNC)

Funding Source: NICHD

Study Contact telephone number: 031-2604684
Study Contact email: Moodleyd1@ukzn.ac.za

What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

Version 4. May 3, 2010

What is the purpose of this study?
The purpose of this research study is to compare two different models of HIV counseling and testing. In one model, women will receive the standard HIV pre and post-test counseling sessions with counselors during their clinical visit. In the other model, women will receive pre and post-test counseling during their clinic visit and two additional HIV counseling sessions at their 6 and 10-week post-partum visits. You are being asked to be in the study because you are a pregnant client at the Umlazi Section D Clinic outside of Durban, South Africa.

Are there any reasons you should not be in this study?
You should not be in this study if you are younger than 18 years. You should not participate in this study if you are not a patient receiving antenatal care at the Umlazi Section D Clinic. You should not be in this study if you are not able to identify a primary partner (as defined by someone you have been in an intimate partnership with for longer than 6-months). You should not be in this study if you do not plan to live in Durban for the next one year. You should also not be in this study if you have previously tested positive for HIV or if you have tested negative for HIV in the last three months.

How many people will take part in this study?
If you decide to be in this study, you will be one of approximately 1,495 women in this research study.

How long will your part in this study last?
If you choose to participate in this study, you will be involved for approximately 1 year. You will have a total of 5 sessions with study team members for either an interview or a counseling session over the course of this one year. For your convenience, we have scheduled the counseling sessions and interviews to coincide with times that you have already scheduled clinic appointments. None of these individual interviews, counseling sessions, or surveys will last longer than 1 hour and a half.

What will happen if you take part in the study?
If you agree to participate, there are a number of things that we would like you to do as part of this study.

1. First, I would like to enroll you in the study. This will take approximately 15 minutes. During enrollment, we will ask if you are willing to share with us information about how to contact you by phone, by mail and in person to remind you of your appointments in this project.

2. Then, we will ask you to complete a baseline interview. This interview will last approximately one hour.

3. Next, you will be randomly assigned to either the intervention or the comparison arm of this study. Random assignment means that you will be assigned to a study group by chance. You will choose an envelope from this basket/box, and the information in the envelope will tell you whether you will be in the intervention arm or the comparison arm of this study. We do not know whether one arm is better than the other. We are

conducting this study to try to compare these two models of HIV counseling and testing. The random assignment process will take approximately 5 minutes to complete.

4. After randomization, you will meet with a nurse today. You will have a pre-test counseling session. At that point you can decide whether you would like to get tested for HIV or not. If you decide you will test for HIV after the pre-test counseling session, you will have your blood drawn for HIV, and you will have a post-test counseling session. The HIV pre and post-test counseling will happen before you receive any other medical services at the clinic today. The HIV counseling and testing will take between 1 hour to 1 hour and a half to complete. If you decide not to test for HIV, this will not affect any of the other services that you can receive at this clinic. You may also decide you would like to test for HIV at a later visit, and that can be arranged.

5. After you complete the HIV counseling and testing, then the nurse will provide your regular ANC visit. During this time, she will take a cervico-vaginal swab from you to test for sexually transmitted infections (STI). If we find that you have a sexually transmitted infection, you will be offered treatment free of charge. The regular visit and STI test will take approximately 1 hour and 15 minutes to complete.

6. In total, it may take you as long as 3 and a half hours to complete today's visit.

7. When you return to the clinic for your 6- and 10-week post-partum visit, after your baby has been born, you will meet with a counselor again at each of these visits. These meetings will last between 30 minutes to 1 hour each.

8. [redacted] complete.

9. 9-months after you have delivered your baby, you will return to the clinic for a final interview. A small number of women who complete this last survey interview will be asked to conduct an additional in-depth interview to learn more about their experiences after they were tested for HIV. The interviews at the 9-month post-partum visit will take between 1 to 1 hour and a half to complete.

10. Trained research team members and/or staff from the Umlazi Section D Clinic will conduct all sessions.

11. In addition, study personnel will look at your medical record after each of your visits with the nurses to learn about your medical information (including your testing decision and whether or not you received ARV prophylaxis if you test positive) and also to review how long each of the counseling sessions took.

Will you receive anything for being in this study?
You will be receiving 50 Rand for taking part in any study visit, including today's visit and the visits: 6 weeks, 10weeks, 14 weeks and 9months after you have delivered your baby. This is to cover the costs of transportation to and from the Umlazi Section D Clinic.

Will it cost you anything to be in this study?
Your costs for participation in this study include only your time.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or concerns, you should contact the researchers listed on the first page of this form.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at the Nelson Mandela School of Medicine, 031 - 260 4769 .

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____
Signature of Research Participant Date

_____
Printed Name of Research Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent

University of North Carolina-Chapel Hill
Isikole Sezifundo Zezokwelapha, i-Nelson R. Mandela, eNyuvesi YaKwaZulu-Natal.
Imvume yokubamba iqhaza ocwaningweni
Abesifazane asebekhulile abaqhamukadult emtholampilo webesifazane (ANC) eMlazi kwa D eThekwini
Enrollment and Baseline Assessment
Ifomu yokuziphatha ngokwenhlalo

Isifundo se-IRB# 07-1070
Ifomu yemvume yangalolo suku: 3 May 2010
Isihloko socwaningo: Efficacy of HIV Post-test Support for ANC in South Africa.
Umcwaningi omkhulu: Usolwazi Suzanne Maman, PhD, MHS
UNC-Chapel Hill Department: Ukuziphatha ngokwezempilo kanye nezifundo ngezempilo
Inombolo yocingo yase-UNC-Chapel Hill: 919-966-3901
E-Mail address: smaman@unc.edu
Abanye abacwaningi:
Usolwazi Dhayendre Moodley (Eningizimu Afrika)
USolwazi Hoosen Coovadia (Eningizimu Afrika)
UDkt. Hannah Sebitloane (Eningizimu Afrika)
UDkt. Ashraf Kagee (Eningizimu Afrika)
UDkt. Prashini Moodley (Eningizimu Afrika)
UDkt. Michael Sweat (MUSC)
UDkt. Shrikant Bangdiwala (UNC)
Nks Allison Groves (UNC)
Nks Petrica Rouse (UNC)

THIS CONSENT DOCUMENT SHOULD BE USED BETWEEN 6-1-10 AND 5-3-11 APPROVED BY INSTITUTIONAL REVIEW BOARD, UNC-CH

Umthombo woxhaso: NICHD
Inombolo yokuxhumana mayelana nocwaningo: 031-260 4684
I-e-mail yokuxhumana mayelana nocwaningo: moodleyd1@ukzn.ac.za

Yiziphi ezinye zezinto okumele uzazi ngezifundo zocwaningo?

Uyacelwa ukuthi ubambe iqhaza esifundweni socwaningo. Ukuzibandakanya kulesi sifundo kuyisenzo sokuzithandela. Unganqaba ukuzibandakanya, noma uhoxise igunya elikubophezela ekutheni ube yingxenye yalesi sifundo nganoma yisiphi isizathu, ngaphandle kokuhlawuliswa.

Izifundo zocwaningo zakhelwe ukuthola ulwazi olusha. Lolu lwazi lungasiza abantu ngokuhamba kwesikhathi. Ungethole lutho oluyinzuzo eqondene nawe ngokuba kulesi sifundo socwaningo. Kanti futhi ukubamba iqhaza kulezi zifundo zocwaningo kungaba nezinkinga zako.

Imininingwane mayelana nalesi sifundo ichaziwe ngezansi. Kubalulekile ukuthi uyiqonde le mininingwane ukuze ukwazi ukuthatha isinqumo owazi kabanzi ngaso ngokubamba

iqhaza kulesi sifundo socwaningo.Uzonikezwa ifomu lokuvuma ukuzibandakanya. Kumele ubuze abacwaningi ababhaliwe ngenhla, noma amalunga abasebenzi abangakusiza ngemibuzo onayo ngalesi sifundo nganoma yisiphi isikhathi.

Iyini inhloso yalesi sifundo?

Inhloso yalesi sifundo ukuqhathanisa izinhlobo ezimbili zokukhanselelwa nokuhlolelwa i-HIV. Ohlelweni olulodwa, abesifazane bazothola ukukhanselwa okwenziwa ngemuva nangaphambi kokuhlolelwa i-HIV okuzokwenziwa amakhansela ngenkathi abesifazane beze emtholampilo. Kolunye uhlelo, abesifazane bazothola ukukhanselwa okwenziwa ngemuva nangaphambi kokuhlolelwa i-HIV ngenkathi beze emtholampilo nezinye futhi izingxoxo zokukhanselwa ezimbili emva kwamasonto ayi-6 kanye nayi-10. Uyacelwa ukuthi ube kulesi sifundo ngoba ungowesifazane okhulelwe ohambela umtholampilo wakwa D eMlazi ngaphandle kwaseThekwini, eNingizimu Afrika.

Ngabe zikhona yini izizathu ezingaholela ekutheni ungabi yingxenye yalesi sifundo?

Awuvumelekile ukuthi ube yingxenye yalesi sifundo uma uneminyaka engaphansi kweyi-18. Awuvumelekile ukuthi ubambe iqhaza kulesi sifundo uma ungahambeli kulo mtholampilo wakwa D eMlazi (ANC). Awuvumelekile ukuba kulesi sifundo uma ungakwazi ukuveza umuntu othandana naye (ochazwa njengomuntu esenibe naye ebudlelwaneni obungaphezu kwezinyanga eziyi-6). Akufanele ube kulesi sifundo uma ungazimisele ukuhlala eThekwini onyakeni owodwa ozayo. Akufanele futhi ube kulesi sifundo uma useke wahlola phambilini wathola ukuthi unayo i-HIV noma uma useke wahlola wathola ukuthi awunayo i-HIV ezinyangeni ezintathu ezedlule.

Bangaki abantu abazobamba iqhaza kulesi sifundo?

Uma unquma ukubamba iqhaza kulesi sifundo, uzoba oyedwa wabesifazane abayi-1,495 kulesi sifundo socwaningo.

Kuzothatha isikhathi esingakanani ukubamba kwakho iqhaza kulesi sifundo?

Uma unquma ukubamba iqhaza kulesi sifundo, uzobandakanyeka unyaka owodwa kuphela. Uyobonana namalunga eqembu lesifundo amahlandla awu-5 okungaba yingxoxo noma ukukhanselwa kuwo lo nyaka owodwa. Ukuze usizakale, sikuhlelele izikhathi lapho uzofika khona uzele izingxoxo zokukhanselwa kanye nezinye izingxoxo (interviews) ukuthi ziqondane nezinsuku lapho uzobe uze lapha emtholampilo. Kuzo zonke lezi zingxoxo (interviews), izingxoxo zokukhanselwa, noma ucwaningo, ngeke kuthathe isikhathi esingaphezulu kwehora 1 nengxenye.

Kuzokwenzakalani uma ubamba iqhaza kulesi sifundo?

Uma uvuma ukubamba iqhaza, kunezinto eziningi esingathanda ukuthi uzenze njengengxenye yalesi sifundo.

1. Okokuqala, ngingathanda ukukubhalisa esifundweni. Lokhu kuzothatha imizuzu eyi-15. Ngenkathi ubhalisa, sizokubuza ukuthi ngabe uzimisele yini ukusinikeza imininingwane yakho lapho sizokuthinta khona ngocingo, nge-email noma wena uqobo ukukukhumbuza ngezikhathi okumele ufike ngazo kule projekthi.

2. Sizobe sesikucela ukuthi uphothule ingxoxo yesisekelo (baseline interview). Le ngxoxo izothatha isikhathi esingangehora elilodwa.

3. Okulandelayo, uzobe usutonyulwa ngokungachemile uyiswe ohlelweni lokungenelela (***intervention)*** noma lokuqhathanisa (***comparison)*** lwalesi sifundo. Ukutonyulwa ngokungachemile kuchaza ukuthi kuzozenzakalela ukuthi uye kulolo hlelo ozoya kulona. Uzokhetha imvilophu kulo bhasikidi/ leli bhokisi, futhi imininingwane kule mvilophu iyona ezochaza ukuthi wena uzoya kuluphi uhlelo lwalesi sifundo. Asinalo ulwazi lokuthi uhlelo oluthile lungcono kunolonye. Siqhuba lesi sifundo ukuzama ukuqhathanisa lezi zinhlobo ezimbili zokuhlolelwa nokukhanselelwa i-HIV. Ukutonyulwa ngokungachemile kuzothatha imizuzu emi-5.

4. Uma usutonyulwe ngokungachemilele, uzohlangana nomhlengikazi namhlanje. Uzoba nengxoxo eba khona ngaphambi kokuhlolwa. Ngaleso sikhathi unganquma ukuthi uyathanda noma cha ukuhlolelwa i-HIV. Uma unquma ukuthi uzohlolelwa i-HIV emva kwengxoxo eba khona ngaphambi kokuhlolwa, kuzothathwa igazi lakho liyohlolelwa i-HIV, uzobe usuba nenye ingxoxo eba khona emva kokuhlolwa. Izingxoxo eziba khona ngaphambi nangemuva kokuhlolelwa i-HIV zizokwenzeka ngaphambi kokuthi uthole olunye usizo lapha emtholampilo namhlanje. Ukukhanselelwa nokuhlolelwa i-HIV kuzothatha phakathi kwehora elilodwa kuya ehoreni elilodwa nengxenye. Uma unquma ukungahlolelwa i-HIV, lokhu ngeke kube namthelela kolunye usizo ongaluthola lapha kulo mtholampilo. Ungaphinde unqume ukuthi uhlolelwe i-HIV ngesinye isikhathi uma usufike lapha emtholampilo, futhi lokho kungahlelwa.

5. Uma usuqedile ukuhlolelwa nokukhanselelwa i-HIV, umhlengikazi uzobe esekunikeza usizo lwe-ANC olujwayelekile. Ngalesi sikhathi, umhlengikazi uzothatha okusaketshezana okusesithweni sangasese sakho ukuze akuhlolele izifo ezithathelanayo zocansi (STI). Uma sithola ukuthi unaso isifo socansi esithathelanayo, uzothola usizo mahhala. Ukufika kwakho lapha nokuhlolelwa ama-STI's kuzothatha ihora elilodwa nemizuzu eyi-15.

6. Sekukonke, kungakuthatha amahora ama-3 nengxenye ukuphothula izinto ozozenza namhlanje.

7. Uma usubuya lapha emtholampilo emasontweni ayi-6 nayi-10 emva kokubeletha, uzohlangana nekhansela futhi kuzo zombili lezi zikhathi. Lezi zingxoxo zizothatha phakathi kwemizuzu engama-30 kuya ehoreni elilodwa ingxoxo ngayinye.

8. Emasontweni ayi-14 emva kokubeletha, uzophinde ubuye uze lapha emtholampilo lapho uzoba khona nenye ingxoxo. Sizophinde sikuhlolele izifo zocansi ezithathelanayo, siphinde sikuhlolele umdlavuza wesibeletho. Lokhu kuzothatha phakathi kwehora elilodwa kuya emahoreni amabili ukukuphothula.

9. Ezinyangeni eziyi-9 emva kokubeletha, uyophinde ubuye uze lapha emtholampilo lapho uyoba nengxoxo yakho yokugcina. Idlanzana labesifazane abaphothula lolu le ngxoxo yokugcina bayocelwa ukuthi babe nenye ingxoxo eyengeziwe ukuthola kabanzi ngezinto abahlangabezana nazo emva kokuhlolelwa i-HIV. Izingxoxo ezinyangeni eziyi-9 emva kokubeletha ziyothatha phakathi kwehora elilodwa kuya ehoreni nengxenye ukuthi ziphele.

10. Amalunga cqembu aqeqeshiwe noma abasebenzi basetholampilo eMlazi kwa D yibona abazobamba zonke lezi zingxoxo.Ukunezezela, abathize balesi sifundo bazobheka imininingwane yakho emayelana nempilo yakho njalo emva kokufika kwakho lapha uze kubahlengikazi ukuthola ngemininingwane emayelana nempilo yakho okubandakanya isinqumo sakho sokuhlolwa nokuthi ngabe uwatholile noma cha ama-ARV uma uthole ukuthi unayo i-HIV nokuthi bathole ukuthi ngabe ingxoxo yokukhanselwa ngayodwa ithathe isikhathi esingakanani.

Ngokusayina lelifomu lemvume namhlanje, ukhombisa ukuthi uyavuma ukubhaliswa, utonyulwe ngokungachemile, ubuzwe imibuzo, uhlolelwe ama-STI's. Uzophinde uthole ukukhanselwa okwenziwa ngaphambi kokuhlolelwa i-HIV futhi ungakhetha ukuthi uhlolelwe i-HIV. Uyophinde unikezwe elinye ifomu lemvume uma usubuya emva kwamasonto ayi-14 emva kokubeletha ukuze uphothule ucwaningo uphinde uhlolelwe ama-STI's.

<u>Yiziphi izinto ongazizuza ngokuba yingxenye yalesi sifundo?</u>

Ungazuza ngokubamba iqhaza kulesi sifundo ngokuthola ithuba lokukhuluma namakhansela aqeqeshiwe ukukulekelela ngenkathi uhlolelwa futhi ukhanselelwa i-HIV. Ungazuza futhi ngokuthola usizo lwamahhala lwezokwelapha ama-STI's uma sithola ukuthi unawo ama STI's. Ungazuza futhi ngokwazi ukuthi imininingwane yalokho ozosixoxela kona namhlanje izosisiza ekuhloleni uhlelo olwenzelwe ukusiza abesifazane abafana nawe kulo mtholampilo.

<u>Yiziphi izinto ezinobungozi noma ezingangenza ngizizwe ngingasakhululekile ngokuzibandakanya kulesi sifundo?</u>

Bukhona ubungozi obungavela uma ungakhuluma ngemininingwane yomunye umuntu kubantu bangaphandle kwaleli thimba locwaningo. Sizozama konke okusemandleni ukukuvikela kulokhu ngokuthi yonke imininingwane siyigcine emakhompyutheni avulwa ngekhodi ethize.
Wonke amakhasethi anemininingwane ayogcinwa emakhabetheni akhiywayo, emahhovisi akhiywayo. Ukunezelela, igama lakho ngeke liqhamuke kulokho okushoyo. Kunokwenzeka futhi ukuthi uma utshela loyo oya naye ocansini ngemiphumela

yokuhlolwa kwakho, uhlangabezane nenkinga ngendlela azoyamukela ngayo imiphumela yakho. Amakhansela aqeqeshiwe azobe ekhona ukukusiza uqhathanise ubuhle nobubi bokuphumela obala ngesimo sakho se-HIV.

Isinqumo sokuphumela obala ngemiphumela yokuhlolwa kwakho kuyisenzo sokuzithandela. Amakhansela azobe ekulungele ukwamukela noma isiphi isinqumo osithathayo. Kunokwenzeka futhi ukuthi ukukhuluma ngezinto eziyimfihlo njengobudlelwane bezocansi, ukuhlelwa komndeni, ne-HIV kungakwenza uzizwe ungakhululekile. Ukulekelelwa ngokomqondo kuzotholakala emtholampilo eMlazi kwa D uma udinga ukukhuluma nomunye nomuntu ngaphandle kwelunga lethimba locwaningo mayelana nalezi zindaba.

Ukubamba kwakho iqhaza kulesi sifundo ngeke kube nomthelela kunoma iluphi usizo olutholayo noma ongase uluthole. Kungenzeka kube nobungozi obungajwayelekile noma obekungalindelekile. Kumele ubike zonke izinkinga elungeni locwaningo. Sizokwazisa ngemininingwane emisha etholakele engaba nomthelela esinqunyeni sakho sokuqhubeka nokubamba iqhaza ngenkathi kuqhutshwa leprojekthi.

Buzovikeleka kanjani ubumfihlo bakho?

Sizozama ngayo yonke indlela ukuvikela ubumfihlo bakho njengomuntu obambe iqhaza kulesi sifundo. Ngeke uvezwe kunoma yimuphi umbiko noma imibhalo yalesi sifundo noma imiphumela yaso. Yonke imininingwane esemakhompyutheni, okubandakanya imibhalo yezingxoxo eziqoshiwe, iyovikelwa ngekhodi eyimfihlo. Ukunezezela, wonke amakhompyutha ayokhiyelwa emahhovisi kanti futhi imininingwane ephathekayo iyogcinwa emafayeleni akhiyiwe. Akukho okuveza imininingwane yomuntu okuyovela engxoxweni noma emibhalweni; kungenjalo, uyonikezwa inombolo yekhodi. Uhla lwamagama namakhodi ahambisanayo kuyogcinwa endaweni engafani nemibhalo futhi iyogcinwa yithimba locwaningo.

Kuyokwenzakalani uma ulimala ulimala kulolu cwaningo?

Kunokuthize okungalungile okungenzeka kuwena kulolu cwaningo. Lokhu kungabandakanya ukulimala. Naphezu kwazo zonke ezokuphepha ezikhona, kungenzeka ulimale noma uvelwe okuthize ngokubamba iqhaza kulesi sifundo. Uma lokhu kwenzeka abacwaningi bayokusiza uthole usizo lwezokwelashwa, kodwa izindleko zokwelashwa ziyobhekana nawe ngqo. INyuvesi ya-Kwa-Zulu Natal kanye neNyuvesi yase-North Carolina kuChapel Hill ayibekanga mali eceleni ukubhekelela lezi zindleko, noma usizo lwezokwelapha oluhlobene naloku. Noma kunjalo, ngokusayina leli fomu, awulahli amalungelo akho ezomthetho.

Ngabe kukhona yini ozokuthola ngokuba kulesi sifundo?

Uzobe uthola amarandi angamashumi amahlanu ngokubamba iqhaza kunoma iyiphi ingxoxo eyingxenye yalesi sifundo, okubandakanya inggxoxo yanamhlanje kanye nezingxoxo esizocela ukuthi sibe nayo nawe emavikini awu 6 nawangu10, nangu 14

nasezinyangeni ezi-9 emva kokubeletha. Le mali eyokukhokhela izinto zokuhamba lapho usuka futhi uya emtholampilo waseMlazi kwa D.

Kukhona yini okuzodingeka ukuthi ukukhokhe ngokubamba iqhaza kulesi sifundo?

Sizodinga isikhathi sakho kuphela kulesi sifundo.

Wenzanjani uma unemibuzo ngalesi sifundo?

Unalo ilungelo lokuthi ubuze, nokuthi uphendulwe yonke imibuzo ongase ube nayo ngalolu cwaningo. Uma unemibuzo, noma izinkinga, kumele uxhumane nabacwaningi ababhalwe ekhasini lokuqala laleli fomu.

Wenzanjani uma unemibuzo ngamalungelo akho njengomuntu obambe iqhaza?

Lonke ucwaningo olwenziwa kubantu luhlolwa yikomidi elisebenzela ukuvikela amalungelo akho. Uma unemibuzo noma izinkinga ngamalungelo akho njengomuntu obambe iqhaza, ungathinta, ngaphandle kokuzazisa uma uthanda, ibhodi lesikhungo esihlolayo (Institutional Review Board) Esikoleni sezemithi iNelson Mandela, 031 – 260 4769.

Imvume yalowo obamba iqhaza

Sengiyifundile imininingwane engiyinikeziwe ngenhla. Sengiyibuzile yonke imibuzo enginayo okwamanje. Ngiyavuma ngokuzithandela ukubamba iqhaza kulesi sifundo socwanigo.

Isiginesha yalowo obamba iqhaza	Usuku
Igama lalowo obamba iqhaza	
Isiginesha yalowo othola iqhaza	Usuku
Igama lalowo othola imvume	

Appendix 6: Copy of Results

Private Bag [illegible] Berlam Road, Maytille, 4058

Patient Name : [redacted] Age: * 30Y 0M 0D
Location : PRINCE MSHIYENI MEMORIAL HOSP./D-CLINIC
Hospital No : 1769/08 Sex/Race: FEMALE/BLACK
Doctor : REFERRING HOSPITAL DOCTOR
Specimen No : 6009054813 Recd Date: 06/08/2009 08:46
Category No : RG /2009/45696 Collt Date: 06/08/2009 08:46
Clinical :
Comment
FOR ENQUIRIES OR FOLLOW UP SPECIMENS PLEASE QUOTE THE PATIENT NUMBER: LB10428612

GYNAE CERVICAL SMEAR ENTER ADDITIONAL SLIDE COUNT(SUBTRACT 1)
GYNAECOLOGICAL REPORT

ADEQUACY

SATISFACTORY FOR EVALUATION.
QUALITY LIMITING FACTOR:
ABSENCE OF ENDOCERVICAL COMPONENT.

CATEGORIZATION

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY.

DESCRIPTIVE INTERPRETATION

CERVICAL SMEAR:
NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY.

NHLS KWAZULU NATAL BRANCH
DEPARTMENT OF
ANATOMICAL PATHOLOGY - CYTOLOGY UNIT
19 OCT 2009
INKOSI ALBERT LUTHULI CENTRAL HOSPITAL

Released By : KHULEKANI MFUNDISI KHUMALO Released Date : 16/10/2009 07:17
Reviewed By : KHULEKANI MFUNDISI KHUMALO Reviewed Date : 16/10/2009 07:17
FOR FURTHER ENQUIRIES PLEASE CONTACT THE LABORATORY ON (031) 240 2630

--END--

NATIONAL HEALTH LABORATORY SERVICE
PROVINCE OF KWAZULU NATAL
INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
DEPARTMENT OF CYTOLOGY
Private Bag - 800 Bellair Road, Mayville, 4058

Patient Name : [redacted]
Location : PRINCE MSHIYENI MEMORIAL HOSP./UMLAZI D
Hospital No : 1409
Doctor : REFERRING HOSPITAL DOCTOR
Specimen No : 6010030785
Category No : RG /2010/27081
Clinical :
Comment

Age: 19Y 7M 20D
Sex/Race: FEMALE/BLACK
Recd Date: 01/04/2010 14:54
Collt Date: 23/03/2010 00:00

FOR ENQUIRIES OR FOLLOW UP SPECIMENS PLEASE QUOTE THE PATIENT NUMBER: LB10537911

GYNAE CERVICAL SMEAR
GYNAECOLOGICAL REPORT

ENTER ADDITIONAL SLIDE COUNT(SUBTRACT 1)

ADEQUACY

SATISFACTORY FOR EVALUATION.
QUALITY LIMITING FACTOR:
ABSENCE OF ENDOCERVICAL COMPONENT.

CATEGORIZATION

SQUAMOUS EPITHELIAL CELL ABNORMALITY.

DESCRIPTIVE INTERPRETATION

CERVICAL SMEAR:
LSIL (LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION) ENCOMPASSING CIN1/HPV INFECTION.

RECOMMENDATION / ADVICE

RECOMMEND A REPEAT SMEAR IN 12 MONTHS FOR FURTHER ASSESSMENT.

Released By : LOVANIA REDDY
Reviewed By : LOVANIA REDDY
Released Date : 21/04/2010 15:43
Reviewed Date : 21/04/2010 15:43
FOR FURTHER ENQUIRIES PLEASE CONTACT THE LABORATORY ON (031) 240 2630

--END--

SOUTH AFRICAN HIV ANTENATAL POSTTEST SUPPORT (SAHAPS) STUDY

MEDICAL CHART EXTRACTION FORM

VISIT: BASELINE (ANTENATAL)

Study Screening #	***S***	***0***	***0***	***1***			
Antenatal Number #							

Date of Visit						
	D	D	M	M	Y	Y

DURATION OF HIV COUNSELING SESSIONS:

1st Post-test Counseling session BASELINE:

Date of 1st post-test counseling session: __ __/__ __/__ __

D D M M Y Y

Time that the consultation started: _____ Time HIV counseling started: _____

Time consultation ended: _____ Time HIV counseling ended: _____

DEMOGRAPHICS

DMG1. Date of Birth?	1. ___ ___ ___ ___ ___ ___ ___ D D M M M Y Y 88. **If DOB unknown: Age (Yrs)** _____
DMG2. Gestational Age at First Antenatal Visit	1. LMP ☐☐ weeks 2. US ☐☐ weeks 3. Palp ☐☐ weeks 4. SFH ☐☐ weeks _____
DMG3. EDD	_ ___ ___ ___ ___ ___ ___ ___ D D M M M Y Y
DMG4. Parity	☐☐
DMG5. Gravidity	☐☐

HISTORY OF SEXUALLY TRANSMITTED INFECTIONS

RISK1. History of STI in the past year	No ☐ Yes ☐ Don't know ☐
RISK2History of Abnormal Vaginal Discharge in the Past Year	Never ☐ Once ☐ Twice ☐ More than twice ☐ Don't know ☐
RISK3. History of genital sore or ulcer in the Past Year.	Never ☐ Once ☐ Twice ☐ More than twice ☐ Don't know ☐

INFANT FEEDING

IF1. Intended feeding method in ANC?	1. exclusive breastfeed ☐ 2. exclusive formula ☐ 3. Other ☐ specify_____ 88. don't know yet ☐

SEXUALLY TRANSMITTED INFECTIONS IN CURRENT PREGNANCY

ST1. STI Lab Investigations Done	RPR ☐ Yes ☐ No TPHA ☐ Yes ☐ No CVS – Neisseria gonorrhea ☐ Yes ☐ No CVS – Trichomonas vaginalis ☐ Yes ☐ No CVS - Chlamydia trachomatis ☐ Yes ☐ No

ST2. STI Lab Investigations Results	RPR ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen TPHA ☐Negative☐Positive ☐Inconclusive ☐Inadequate Specimen CVS – N. gonorrhea ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen CVS T. vaginalis ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen CVS C. trachomatis ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen
ST3. Clinical Signs of STI (Discharge/ulcer etc)	☐Yes ☐ No
ST4. PAP smear done	☐ Yes ☐ No
ST5. If Yes	Results

HIV RELATED

HR1. HIV Tested Today	☐Yes ☐ Refused **If Yes SKIP to HR2.**
HR2. If refused, why?	☐ Did not perceive herself to be at risk ☐ Afraid to test ☐ Tested before ☐ To discuss with partner ☐ Other _____ **SKIP to Infant Feeding CP1**
HR2. HIV Test Result Today	☐Negative ☐Positive ☐Inconclusive **If Negative skip to CP1**
HR3. If Positive, ……	➢ CD4 Test Done ☐ Yes ☐ No ➢ Clinical Staging Done ☐ Yes ☐ No ➢ NVP Dispensed ☐ Yes ☐ No ➢ MVT Dispensed ☐ Yes ☐ No ➢ AZT Dispensed ☐ Yes ☐ No

HR4. Results	➢ CD4 Test Result ☐☐☐☐☐ ➢ Clinical Staging ☐☐ ➢ Date NVP Dispensed __ __/__ __/__ __ D D M M Y Y ➢ Date MVT Dispensed __ __/__ __/__ __ D D M M Y Y ➢ Date AZT Dispensed __ __/__ __/__ __ D D M M Y Y

SOUTH AFRICAN HIV ANTENATAL POSTTEST SUPPORT (SAHAPS) STUDY

MEDICAL CHART EXTRACTION FORM

VISIT: 6 WEEK (POSTNATAL)

Study Screening #	***S***	***0***	***0***	***1***			
Antenatal Number #							

Date of Visit						
	D	D	M	M	Y	Y

DURATION OF HIV COUNSELING SESSIONS:

2nd Post-test Counseling session 6 WEEK:

Date of 2nd post-test counseling session: __ __/__ __/__ __

D D M M Y Y

Time that the consultation started: _____ Time HIV counseling started: _____

Time consultation ended: _____ Time HIV counseling ended: _____

INFANT HEALTH

IH1. Infant's Condition	☐Alive ☐ Demised **If demised SKIP to SB1 (SEXUAL BEHAVIOUR)**
IH2. Baby Weight	☐☐.☐ kg
IH3. Is infant fully immunized to-date?	☐Yes ☐No
IH4. Infant Feeding Practice	☐ Exclusive breastfeed ☐ Exclusive formula ☐ Breast and Other ☐ Formula and Other ☐ Breast and Formula
IH5. Is infant HIV Exposed?	☐Yes ☐No **If No skip to SB1 (SEXUAL BEHAVIOUR).**
IH6. If Infant is HIV Exposed, was Bactrim Administered?	☐Yes ☐No
IH7. If Infant is HIV Exposed, was Infant tested by PCR for HIV?	☐Yes ☐No

SEXUAL BEHAVIOUR

SB1. Since delivery have you had sex?	☐Yes ☐No **If No skip to SB6**

SB2. When did you first have sex since delivery?	☐1 ☐2 ☐3 ☐4 ☐5 **weeks after birth**
SB3. Since delivery how many times have you had sex?	☐☐ ☐ times
SB4. How many times have you used a condom?	☐☐ ☐ times
SB5. What method or methods of Contraception is she on?	☐Pill ☐Injectables ☐Male condom ☐Female condom ☐Tubal Ligation ☐Other_specify_____
SB6. Have you shared your HIV test results with your partner?	☐Yes ☐No
SB7. Since you have tested for HIV, has your partner been tested for HIV?	☐Yes ☐No **If No skip to DB1 (DELIVERY-BIRTH)**
SB8.What are his Test Result	☐Positive ☐Negative ☐ Do not know

DELIVERY-BIRTH OUTCOMES

DB1. Date of Delivery	1. ___ ___ ___ ___ ___ ___ ___ D D M M M Y Y
DB2. Gender of Baby	☐ male ☐ female ☐ N/A
DB3. Pregnancy Outcome	☐ FSB ☐ MSB ☐ LB ☐ ENND
DB4. Baby Birth Weight	☐☐.☐kg
DB5. Infant Feeding Practice at Birth	☐ Exclusive breastfeed ☐ Exclusive formula ☐ Breast and Other ☐ Formula and Other ☐ Breast and Formula ☐ N/A
DB6. sd NVP Administered to Mum in Labour	☐Yes ☐No ☐ N/A
DB7. sd NVP Administered to Infant at Birth	☐Yes ☐No ☐ N/A
DB8. AZT Administered during Labour	☐Yes ☐No ☐ N/A
DB9. AZT Administered to Infant	☐7DAYS ☐28DAYS ☐NONE ☐N/A
DB10. NVP Administered to *Infant for 6 weeks*	☐Yes ☐No ☐ N/A
DB11. HAART Initiated	☐Yes ☐No ☐ N/A
DB12. Date HAART Initiated	D D M M M Y Y ☐ N/A

SOUTH AFRICAN HIV ANTENATAL POSTTEST SUPPORT (SAHAPS) STUDY

MEDICAL CHART EXTRACTION FORM

VISIT: 14 WEEK (POSTNATAL)

Study Screening #	***S***	***0***	***0***	***1***			
Antenatal Number #							

Date of Visit						

SEXUALLY TRANSMITTED INFECTIONS POSTNATALLY

ST1. STI Lab Investigations Done	**RPR** ☐ Yes ☐ No **TPHA** ☐ Yes ☐ No **CVS – Neisseria gonorrhea** ☐ Yes ☐ No **CVS – Trichomonas vaginalis** ☐ Yes ☐ No **CVS - Chlamydia trachomatis** ☐ Yes ☐ No
ST2. STI Lab Investigations Results	**RPR** ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen **TPHA** ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen **CVS – N. gonorrhea** ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen **CVS T. vaginalis** ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen **CVS C. trachomatis** ☐Negative ☐Positive ☐Inconclusive ☐Inadequate Specimen
ST3. Clinical Signs of STI (Discharge/ulcer etc)	☐ Yes ☐ No
ST4. PAP smear done	☐ Yes ☐ No
ST5. If Yes	Results

HIV RETESTING FOR WOMEN WHO TESTED NEGATIVE AT LAST TEST

HR1. HIV Tested Today	☐Yes ☐ Refused **If Yes SKIP to HR2.**

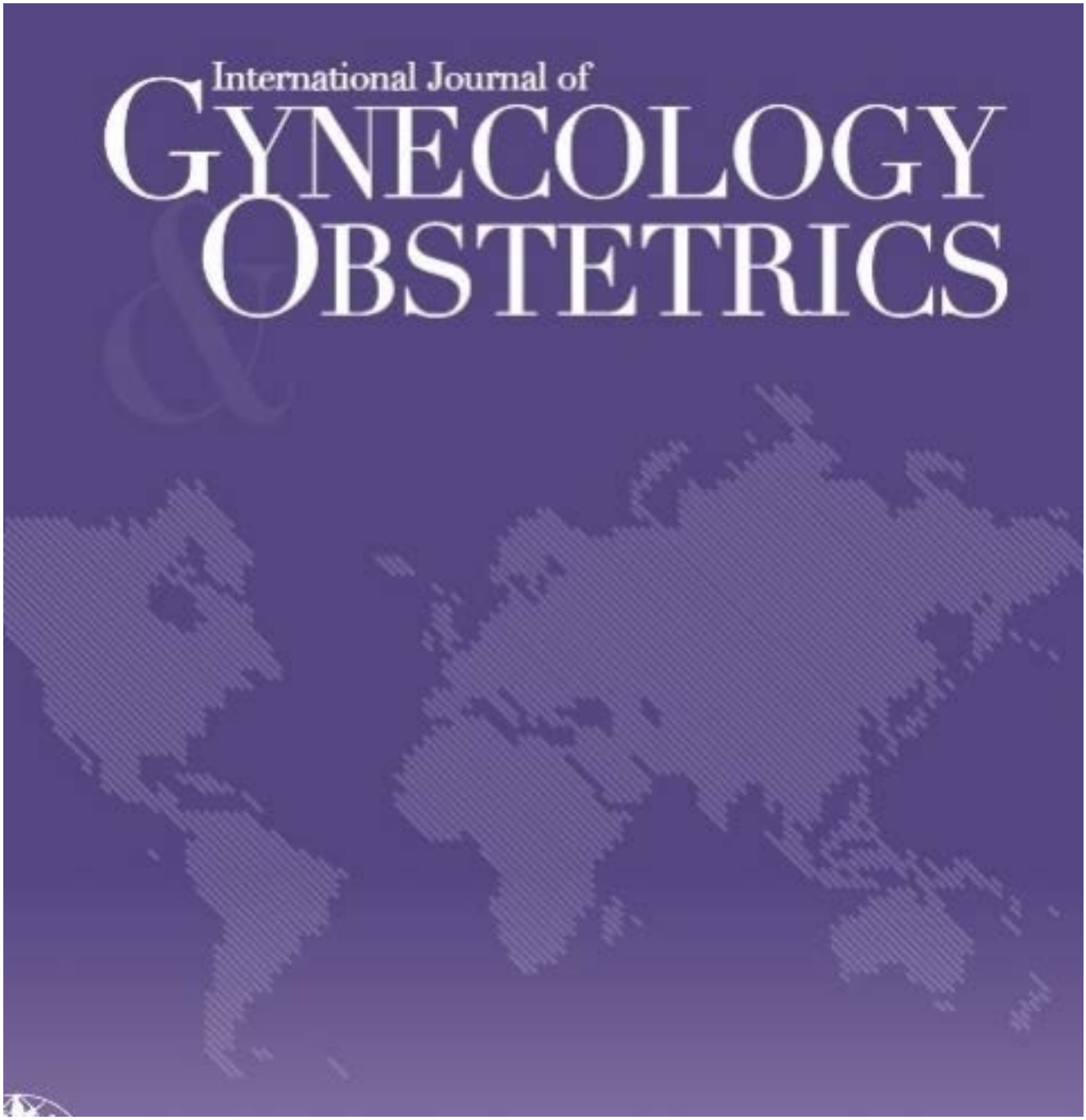
HR2. If refused, why?	☐ Did not perceive herself to be at risk ☐ Afraid to test ☐ Tested before ☐ To discuss with partner ☐ Other _____ **SKIP to Infant Feeding CP1**
HR2. HIV Test Result Today	☐Negative ☐Positive ☐Inconclusive **If Negative skip to CP1**
HR3. If Positive, ……	➢ CD4 Test Done ☐ Yes ☐ No ➢ Clinical Staging Done ☐ Yes ☐ No ➢ NVP Dispensed ☐ Yes ☐ No ➢ HAART Initiated ☐ Yes ☐ No
HR4. Results	➢ CD4 Test Result ☐☐☐☐☐ ➢ Clinical Staging ☐☐ ➢ Date NVP Dispensed __ __/__ __/__ __ D D M M Y Y ➢ Date MVT Dispensed __ __/__ __/__ __ D D M M Y Y ➢ Date AZT Dispensed __ __/__ __/__ __ D D M M Y Y ➢ Date HAART Dispensed __ __/__ __/__ __ D D M M Y Y

INFANT HEALTH

IH1. Infant Feeding Practice	☐ Exclusive breastfeed ☐ Exclusive formula ☐ Breast and Other ☐ Formula and Other ☐ Breast and Formula

DB1. NVP Administered to Infant	☐Yes ☐No ☐ N/A

APPENDIX 8: PUBLISHED MANUSCRIPT



Article Type: Clinical Article

Prevalence, risk factors, and pregnancy outcomes of cervical cell abnormalities in the puerperium in a hyperendemic HIV setting

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[2] Department of Health Behavior, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, USA

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Keywords: Birth outcomes; HIV; Pap smear; Puerperium; Squamous cell abnormalities

Synopsis: HIV-infected pregnant women are likely to present with higher grades of cervical cell abnormalities in the puerperium but without any evidence of adverse pregnancy outcomes.

ABSTRACT

Objective: To investigate the impact of cervical cell abnormalities detected in the puerperium in association with HIV-1 infection on pregnancy outcomes.

Methods: The present study was a secondary data analysis of pregnancy outcomes, Pap smear results, HIV results, and participant demography from a behavioral intervention randomized controlled trial of 1480 pregnant women aged 18 years or more conducted at a periurban primary health clinic in South Africa during 2008–2010. The Pap smear was performed 14 weeks after delivery.

Results: In total, 564 (38.1%) women were HIV-1-positive and 78 (8.0%) of 973 women with a categorized Pap smear result tested positive for cervical cell abnormalities; 42 (4.2%) women had low-grade squamous intraepithelial lesions (LGSILs) and 7 (0.7%) had high-grade lesions (HGSILs). In an adjusted analysis, HIV infection was significantly more common among women with LGSILs (28/42 [66.7%]) or HGSILs (6/7 [85.7%]) when compared with the other Pap smear categories ($P<0.001$). The rates of premature birth, low birth weight, and non-live births were similar among HIV-infected and -uninfected women with abnormal cervical cytology.

Conclusion: Pregnant women with HIV were more likely to be diagnosed with higher grades of squamous cell abnormalities than those without HIV. There was no association between squamous cell abnormalities/HIV comorbidity and adverse pregnancy outcomes.

1 INTRODUCTION

In 2015 alone, an estimated 526 000 new cases of cervical cancer were reported globally, and in the same year, an estimated 239 000 women died from the disorder [1]. Cervical cancer is the leading cause of cancer-related death in women in most parts of Sub-Saharan Africa [1]. Persistent infection with a high-risk type of HPV is associated with the disease: of the 15 high-risk types, HPV-16 and HPV-18 account for 70% of cases of cervical cancer [2].

Cervical cytology and HPV testing are currently the most effective screening tools used in the prevention of cervical cancer [3]. Cervical cancer precursors can be detected by cervical cytology, commonly known as the Papanicolaou (Pap) test. Consistent evidence indicates that HIV-positive women have a higher prevalence of HPV infection, the infection is more persistent, and the prevalence of pre-invasive cervical lesions is higher [4]. In 2014, cervical cancer was ranked in the top 10 causes of death among women in South Africa, which is also one of the four countries globally with the highest HIV prevalence in women of reproductive age [5,6]. Moreover, there is growing evidence of a high prevalence of high-risk HPV infection and cervical intraepithelial neoplasia (CIN) 2/3 among HIV-infected women of reproductive age in South Africa [7,8].

Studies of cervical lesions in pregnancy are sparse, and the available studies report a low but a wide range of prevalences of cervical cancer (0.1–12 per 10 000 pregnancies) and CIN (0.13–0.27 per 10 000 pregnancies) [9,10]. There is no evidence that pregnancy itself increases the rate of CIN progression to invasive carcinoma [11,12]. Pregnancy outcomes have also been reported as unaltered by

cervical cancer or CIN [9]. A multivariable analysis of more than 3000 women with a HPV prevalence of 10% concluded that HPV was not an independent risk factor for preterm delivery [13].

Many previous studies were conducted in settings with a low prevalence of HIV, and it is becoming increasingly evident that HIV-positive pregnant women are more likely to have a high prevalence of HPV and pre-invasive cervical lesions [14,15]. Although HIV is independently associated with adverse pregnancy outcomes, to our knowledge, there are no studies that have evaluated pregnancy outcomes in women with HIV and HPV infection/CIN [16]. In the present study, we investigated the impact of cervical squamous cell abnormalities in association with HIV infection on pregnancy outcomes.

2 MATERIALS AND METHODS

The South Africa HIV/AIDS Post-test Support (SAHAPS) study, a randomized controlled trial of a behavioral intervention, enrolled 1480 pregnant women at a periurban primary health clinic in Durban, South Africa, between May 1, 2008, and June 30, 2010. Women were eligible for enrollment if they were 18 years or older, had a current intimate partner, and intended to continue with postnatal/child immunization at the same facility. All women received basic prenatal care, HIV testing and counselling, and screening for sexually transmitted infections (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) in pregnancy. Women were reassessed at 6, 10, and 14 weeks, and at 9 months after delivery. A Pap smear was performed at the postpartum visit at 14 weeks and sent to the routine laboratory services for cytology.

The main findings of the SAHAPS study have been published previously [17]. We performed a secondary data analysis of select variables such as pregnancy outcomes, Pap smear results, HIV results, and patient demography extracted from the parent database. The study was approved by the institutional review boards of the University of KwaZulu-Natal, Durban, South Africa, and the University of North Carolina at Chapel Hill, NC, USA. Written informed consent was obtained from all women who participated in the main study.

Cervical smears were obtained through the standard method [18]. Smears were analyzed by the cytological laboratory using microscopy after Pap staining. The Bethesda classification [19] was used to report the findings. Patients were managed in accordance with the standard protocol for low-grade squamous intraepithelial lesions (LGSILs) and atypical squamous cells of undetermined significance (ASCUS), for which a repeat Pap smear is recommended after 6–12 months. Women with high-grade squamous intraepithelial lesions (HGSILs) were referred for colposcopy. The present data are limited to the screening phase and thus do not include the management of lesions.

Births occurring before 37 weeks of pregnancy were defined as preterm. The pregnancy duration was determined by obstetric measurements and in the absence of ultrasonography done before 24 weeks; an average measure obtained on the basis of symphysis fundal height, last menstrual date, and palpation was used to estimate the pregnancy duration at the first prenatal visit. A low birth weight was defined as a weight of less than 2500 g in term deliveries (pregnancy duration ≥37

weeks), and a stillbirth was defined as fetal demise at a pregnancy duration of 21 weeks or more. A spontaneous abortion was defined as fetal demise before 21 weeks.

The data were analyzed using Stata 13.0 SE (StataCorp, College Station, TX, USA). Ninety-five percent confidence intervals (CIs) were constructed around prevalence point estimates (prevalence of CIN in the puerperium). The association between continuous demographic and clinical characteristics with CIN status was assessed using the standard *t* test or the nonparametric Wilcoxon rank-sum test if the normality assumption was not upheld. Differences in frequencies of categorical demographic or clinical characteristics by CIN status and associations with perinatal outcomes were assessed using the Pearson χ^2 test or the Fisher exact test if an expected cell count contained fewer than five observations. Multivariable logistic regression was employed to assess factors associated with CIN after controlling for the confounding influence of other covariates. Model fit and validity were confirmed. $P<0.05$ was considered statistically significant.

3 RESULTS

Of the 1480 pregnant women enrolled in the SAHAPs study, 564 (38.1%, 95% CI 35.7%–40.1%) women tested HIV-positive at their first prenatal visit. Pap smear results were not available for 471 (31.8%) women in this cohort. Among the 1009 women who had a Pap smear result in the postpartum period, categorization was not possible for 36 (3.6%) and 895 (88.7%) women had normal smears. The HIV prevalence (n=317 [31.4%] vs n=153 [32.5%]; *P*=0.720), age distribution (n=504 [50.0%] vs n=245 [52.0%] <25 years; *P*=0.468), prevalence of non-live births (n=38

[3.8%] vs n=18 [3.8%]; *P*>0.999), prevalence of preterm births (n=191 [18.9%] vs n=89 [18.9%]; *P*=0.942), and prevalence of a low birth weight (n=42 [4.2%] vs n=14 [3.0%]; *P*=0.205) were comparable between women who had a Pap smear result and those who did not.

Of the 973 women with a categorized Pap smear result at the postpartum visit, 78 (8.0%; 95% CI 6.4%–9.9%) women tested positive for squamous cell abnormalities. Abnormalities included 29 (2.9%; 95% CI 2.0%–4.1%) atypical (ASCUS) cases, 42 (4.2%, 95% CI 3.1%–5.6%) cases of LGSILs or HPV infection, and 7 (0.7%; 95% CI 0.3%–1.4%) cases of HGSILs. The mean age of women presenting with some form of squamous cell abnormality was 24.9 ± 4.9 years, which did not differ significantly from the mean age of women with no abnormalities (25.7 ± 5.4 years). The proportion aged 24 years or older was higher among women with HGSILs than among those with LSILs, but the difference between all groups was not significant in adjusted analyses (*P*=0.548) (Table 1).

Multivariable analysis indicated that HIV infection was significantly more common among women presenting with LGSILs (66.7%) or HGSILs (85.7%) than in other groups (*P*<0.001) (Table 1). Of the 1009 women with a Pap smear result, 34 (3.4%) were HIV-positive and also had squamous cell abnormalities. Moreover, the proportion of women with at least one previous pregnancy was significantly higher among those with HGSILs than among other groups (*P*=0.023) (Table 1).

Pregnancy outcome data were available for 792 (78.5%) of the 1009 women with a Pap smear result. There were 8 (1.0%, 95% CI 0.5%–2.0%) spontaneous abortions,

17 (2.1%, 95% CI 1.3%–3.4%) stillbirths, 767 (96.4%, 95% CI 94.8%–97.5%) live births, and 4 (0.5%, 95% CI 0.2%–1.2%) neonatal deaths. Among the 767 live births, 131 (17.1%, 95% CI 14.7%–19.9%) were premature and 30 (3.9%, 95% CI 2.8%–5.9%) newborns were of low birth weight. There were no birth weight and preterm data for 144 (18.8%) and 3 (0.4%) live births, respectively.

Live birth occurred for 292 (96.4%) of 303 women with HIV infection and 475 (97.1%) of 489 women without HIV infection (*P*=0.343). Among the live births, the frequencies of preterm births were also not significantly different between women with and without HIV infection (n=49 [16.8%] vs n=82 [17.3%]; *P*=0.473). However, low neonatal birth weight was more common among women with HIV infection (n=14 [4.8%]) than among those without this disorder (n=11 [2.3%]; *P*=0.049).

In a separate bivariate analysis (Table 2), birth outcomes were compared between women with and without cytological abnormalities. No marked differences in the prevalences of low birth weight and non-live births in these comparator groups were identified. Although the proportion of preterm births was higher among women with HGSILs as compared with women with LGSILs, ASCUS, or normal cytology, this association was not statistically significant (*P*=0.222).

In comparing the pregnancy outcomes among HIV-infected and HIV-uninfected women with a cytological abnormality, the rates of premature birth, low birth weight, and live birth were similar across all groups (Table 3). The frequency of a low birth weight was, however, significantly higher among HIV-positive women with a normal

cytological result when compared with their HIV-negative counterparts (*P*=0.026) (Table 3).

4 DISCUSSION

A Pap smear routinely performed approximately 3 months after delivery revealed cervical squamous cell abnormalities in 8% of the study population. Notably, older women with one or more previous pregnancies were more likely to be diagnosed with HGSILs, whereas younger women were more likely to present with atypical squamous cell appearance or LGSILs. We can also confirm that HIV-1 infection was certainly related to LGSIL or HGSIL detected after delivery, with the prevalence of HGSILs among women with HIV comorbidity being less than 2%. We believe this is the first study to determine the effect of cervical lesions in combination with HIV infection on pregnancy outcomes. Although the presence of cervical lesions by itself has not previously been associated with poor birth outcomes, the underlying pathogenesis of HPV infection has been associated with preterm birth [9,20]. In the present study, where we expected HIV-positive women with LGSILs or HGSILs to have worse pregnancy outcomes than HIV-uninfected women with LGSILs or HGSILs, there was no evidence of this association and neither was this evident for LGSIL or HGSIL alone.

A limited number of studies of pregnant women reported the prevalence of CIN in pregnancy to range between 1% and 5% [9,21]. Methodological variations in diagnosis and social determinants are possible reasons for the heterogeneous prevalence rates. Infection with HPV is known to be the necessary cause of CIN; hence, molecular techniques such as HPV DNA and HPV mRNA tests are likely to

yield a higher prevalence of CIN 1 [22]. Conventional cytology is known to be less sensitive, and in the majority of the studies abnormal cytology results were largely classified as ASCUS. In such cases, high-risk HPV DNA tests are more likely to identify CIN 1 [22]. Using conventional cytology as a routine screening test in the present study population still yielded a higher proportion of women (5.0%) with low-grade or high-grade lesions, and if the atypical cytology results are included, the prevalence of abnormal cervical cytology in the present population is likely to be approximately 8.0%.

The timing of screening in pregnant women could be another potential reason for varying prevalence rates. Some studies presented findings from screening in pregnancy, whereas other studies—including the present study—have presented findings from screening in the postpartum period [23]. However, there is evidence that noninvasive CIN diagnosed in pregnancy has a tendency not to progress during pregnancy, and 48%–70% of cases have regressed to complete remission after delivery [11,12]. Only high-grade CIN is more likely to persist after delivery, and the present prevalence of HGSILs in postpartum women (0.7%) is higher than that in most other reported studies of pregnant women (0.4%) [23]. A large population-based study in Brazil [14] confirmed that the prevalence of HGSILs (0.4%) in pregnant women was similar to that in their nonpregnant counterparts. There are few studies that have investigated the association between CIN and HIV in pregnancy, but most studies did not compare their findings with an HIV-uninfected group of pregnant women [14,15]. In the present study, when compared with women with a normal Pap smear, the prevalence of HIV infection was twofold higher in women with LGSILs and almost 2.5 times higher among women with HGSILs after delivery. This

association between HIV and cytological abnormalities is consistent with findings from two other South African studies of nonpregnant women and could mainly be related to an increased persistence of high-risk HPV infections in HIV-infected women [8,24].

Generally, infections and associated morbidity in pregnancy are likely to alter pregnancy outcomes. Yet, there was no evidence of greater adverse pregnancy outcomes among HIV-infected women with cervical cell abnormalities in the present South African study cohort. Only a handful of studies have reported pregnancy outcomes for a population with cervical cell abnormalities, and none of these explored the outcomes in pregnant women with HIV coinfection. Findings from these limited studies were indicative of an association between preterm delivery and CIN/HPV infection. The present findings appear reassuring and indicate that HIV and LGSIL or HGSIL do not alter pregnancy outcomes. We have previously shown that untreated sexually transmitted infections in pregnancy could contribute to adverse pregnancy outcomes [25].

There are several limitations to the present study as a result of it being a retrospective data analysis. These limitations include missing pregnancy outcome data, missing Pap smear results for a large proportion of the study population, and lack of quality control measures in the performance of Pap smears.

In conclusion, the present findings confirm that HIV-infected postpartum women are more likely to be diagnosed with higher grades of cervical cell abnormalities, compared with postpartum women without HIV infection. Given the low prevalence of

HGSILs at the postpartum visit and the lack of an association between birth outcomes and HGSIL/HIV comorbidity, cervical screening may be postponed to the postpartum period but remains essential. There is also a need for additional studies to review the impact of the recently introduced national HPV vaccination program in South Africa.

Author contributions

HCM conceptualized the present substudy, interpreted the statistical analysis, and wrote the manuscript. DM assisted in the conceptualization of the substudy and the interpretation of the statistical analysis, and helped to write the manuscript. BS performed the statistical analysis and contributed to the development of the manuscript. MS assisted with the data interpretation and the editing of the manuscript. SM was the principal investigator of the primary study and edited the manuscript.

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Conflicts of interest

The authors have no conflicts of interest.

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Table 1 Characteristics of women with and without squamous cell abnormalities in the puerperium.[a]

Characteristic	ASCUS (n=29)	Diagnosis deferred (n=36)	HGSILs (n=7)	LGSILs (n=42)	Normal Pap smear (n=895)	Unadjusted *P* value	Adjusted *P* value [b]
Age, y						0.072	0.548
<24	18 (62.1)	22 (61.1)	1 (14.3)	24 (57.1)	436 (48.7)		
≥24	11 (37.9)	14 (38.9)	6 (85.7)	18 (42.9)	459 (51.3)		
Education						0.405	0.749
No formal school	3 (10.3)	1 (2.8)	0	1 (2.4)	54 (6.0)		
Primary	9 (31.0)	13 (36.1)	5 (71.4)	18 (42.9)	368 (41.1)		
Secondary	17 (58.6)	22 (61.1)	2 (28.6)	23 (54.8)	472 (52.7)		
Missing	0	0	0	0	1 (0.1)		
Socioeconomic status						0.709	0.503
Low	11 (37.9)	15 (41.7)	2 (28.6)	16 (38.1)	338 (37.8)		
Moderate	12 (41.4)	13 (36.1)	3 (42.9)	19 (45.2)	339 (37.9)		
High	5 (17.2)	8 (22.2)	2 (28.6)	6 (14.3)	197 (22.0)		
Missing	1 (3.4)	0	0	1 (2.4)	21 (2.3)		
Previous pregnancies						0.035	0.023
0	17 (58.6)	1 (2.8)	1 (14.3)	17 (40.5)	310 (34.6)		
1–2	6 (20.7)	4 (11.1)	4 (57.1)	19 (45.2)	329 (36.8)		
≥3	6 (20.7)	2 (5.6)	2 (28.6)	6 (14.3)	256 (28.6)		
Missing	0	29 (80.6)	0	0	0		
HIV status						<0.001	<0.001
Negative	18 (62.1)	25 (69.4)	1 (14.3)	14 (33.3)	570 (63.7)		
Positive	11 (37.9)	11 (30.6)	6 (85.7)	28 (66.7)	325 (36.3)		
Neisseria gonorrhoeae						0.766	0.714
Negative	28 (96.6)	32 (88.9)	6 (85.7)	39 (92.9)	836 (93.4)		
Positive	1 (3.4)	4 (11.1)	1 (14.3)	2 (4.8)	48 (5.4)		
Missing	0	0	0	1 (2.4)	11 (1.2)		
Chlamydia trachomatis						>0.99	0.412
Negative	25 (86.2)	30 (83.3)	6 (85.7)	34 (81.0)	723 (80.8)		
Positive	4 (13.8)	6 (16.7)	1 (14.3)	8 (19.0)	161 (18.0)		
Missing	0	0	0	0	11 (1.2)		
Trichomonas vaginalis						0.654	0.893
Negative	26 (89.7)	30 (83.3)	5 (71.4)	36 (85.7)	761 (85.0)		
Positive	2 (6.9)	6 (16.7)	2 (28.6)	6 (14.3)	123 (13.7)		
Missing	1 (3.4)	0	0	0	11 (1.2)		

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HGSIL, high-grade squamous intraepithelial lesion; LGSIL, low-grade squamous intraepithelial lesions.

[a] Values are given as number (percentage) unless indicated otherwise.

[b] Adjusted for age group, education, socioeconomic status, and presence of other sexually transmitted infections (as appropriate).

Table 2 Pregnancy outcomes among 792 women with and without squamous cell abnormalities in the puerperium.[a]

Pregnancy outcome	ASCUS (n=26)	HGSILs (n=7)	LGSILs (n=33)	Normal Pap smear (n=726)	Unadjusted *P* value
Birth outcome					0.918
Spontaneous abortion	0	0	1 (3.0)	7 (1.0)	
Stillbirth	1 (3.8)	0	0	16 (2.2)	
Live birth	25 (96.2)	7 (100.0)	32 (97.0)	703 (96.8)[b]	
Birth weight [c]					0.403
<2500 g	3 (12.0)	2 (28.6)	0	25 (3.6)	
≥2500 g	21 (84.0)	5 (71.4)	31 (96.9)	536 (76.2)	
Missing	1 (4.0)	0	1 (3.1)	142 (20.2)	
Pregnancy duration at delivery [c]					0.552
Preterm (<37 wk)	4 (16.0)	3 (42.9)	4 (12.5)	120 (17.1)	
Term (≥37 wk)	21 (84.0)	4 (57.1)	28 (87.5)	580 (82.5)	
Missing	0	0	0	3 (0.4)	

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HGSIL, high-grade squamous intraepithelial lesions; LGSIL, low-grade squamous intraepithelial lesions.
[a] Values are given as number (percentage) unless indicated otherwise.
[b] Includes 4 neonatal deaths.
[c] Among live births.

Table 3 Pregnancy outcomes among 792 women with and without squamous cell abnormalities and/or HIV infection in the puerperium.[a]

Pregnancy outcome	ASCUS			HGSILs			LGSILs			Normal Pap smear		
	HIV + (n=11)	HIV – (n=15)	*P* value	HIV + (n=6)	HIV – (n=1)	*P* value	HIV + (n=21)	HIV – (n=12)	*P* value	HIV + (n=265)	HIV – (n=461)	*P* value
Birth outcome			0.576			—			0.364			0.176
No live birth	0	1 (6.7)		0	0		0	1 (8.3)		11 (4.2)	12 (2.6)	
Live birth	11 (100.0)	14 (93.3)		6 (100.0)	1 (100.0)		21 (100.0)	11 (91.7)		254 (95.8)	449 (97.4)	
Birth weight [b]			—			—			—			0.032
<2500 g	0	0		0	0		0	0		14 (5.5)	11 (2.4)	
≥2500 g	7 (63.6)	13 (92.9)		4 (66.7)	0		16 (76.2)	11 (100.0)		190 (74.8)	346 (77.1)	
Missing	4 (36.4)	1 (7.1)		2 (33.3)	1 (100.0)		5 (23.8)	0		50 (19.7)	92 (20.5)	
Pregnancy duration at delivery [b]			0.209			0.429			0.166			0.288
Preterm (<37 wk)	3 (27.3)	1 (7.1)		2 (33.3)	1 (100.0)		4 (19.0)	0		40 (15.7)	80 (17.8)	
Term (≥37 wk)	8 (72.7)	13 (92.9)		4 (66.7)	0		17 (81.0)	11 (100.0)		212 (83.5)	368 (82.0)	
Missing	0	0		0	0		0	0		2 (0.8)	1 (0.2)	

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HGSIL, high-grade squamous intraepithelial lesions; LGSIL, low-grade squamous intraepithelial lesions.

[a] Values are given as number (percentage) unless indicated otherwise.

[b] Live births only.