THE PERFORMANCE OF THE REID COLPOSCOPIC INDEX AND SWEDE SCORE: PREDICTING CIN IN WOMEN LIVING WITH HIV-1 IN SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology.

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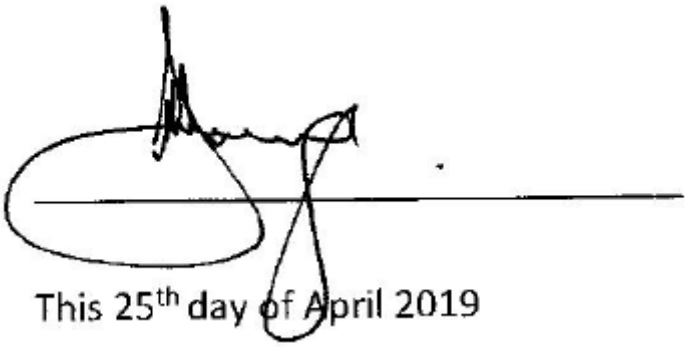
Declaration

I Vusumuzi David Maringa declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



This 25th day of April 2019

Abstract

Background and objectives

Cervical cancer can be prevented by screening and treatment of cervical cancer precursor lesions. Women with an abnormal Pap smear are referred to colposcopy for diagnosis and are then treated immediately in many South African colposcopy clinics.

Hence accurate colposcopic diagnosis is important. The aim of this study was to determine the accuracy of diagnosing cervical intraepithelial neoplasia with either the Reid Colposcopic Index or the Swede score in HIV infected women. The components of the Reid colposcopic index are acetowhiteness, margins, vascular patterns and iodine staining. The Swede score has all the components of the Reid score with the addition of lesion size as a fifth component.

Methods

This was a secondary data analysis of the South African arm of the "HPV in Africa Research Partnership (HARP) study" comparing different screening tests in the prevention of cervical cancer in HIV infected women. Women were recruited from primary health care clinics and HIV treatment centres in Hillbrow, Johannesburg. All women had a Pap smear, Human papillomavirus testing, and visual inspection with lugol's iodine and with acetic acid. All women with any positive screening test were referred to colposcopy. At colposcopy a four-quadrant biopsy and directed biopsies of any visible lesions were performed. The colposcopist recorded the colposcopy findings using the Swede score. For this study, the information from the Swede score was used to determine the Reid colposcopy index. Data was extracted from the HARP study database.

Results

A total of 624 women were eligible for the study in the South African arm, only 577 women were included for this study.

The mean age was 34 years (SD±5.89). Antiretroviral therapy was used by 370 (64%) women. Abnormal Pap smears were found in 484 (88%) women, VIA was positive in 162

(28%), VILI was positive in 219 (37%) and HR HPV DNA was found in 374 (65%) women respectively.

Histological findings showed that 263 (46%) of the women had no CIN, 185 (32%) had CIN 1, 76 (13%) had CIN 2 and 53 (9%) had CIN 3. The Swede score of 5 had a sensitivity of 72.9%, specificity of 71.9%, PPV of 42.7%and NPV of 90.2% respectively. A Reid score of 4 had a sensitivity of 72.9%, specificity of 69.4%, PPV of 40.7% and NPV of 89.9%. In comparison, the Area under the curve was higher for the Swede score compared to the Reid and this difference was statistically significant.

Conclusion

This study shows that the Swede score when compared to the Reid score performs better in terms of accuracy for predicting CIN≥2 lesions. The addition of the lesion size has been shown to have an added advantage in the performance of the scoring. Both scores also demonstrated flexibility. There is a higher likelihood of HIV infected women to be referred for colposcopy as they have a higher incidence of cervical cancer precursor lesions. There was no difference in the performance of the Swede or Reid score by antecedent Pap smear and there was no difference in colposcopy findings on women with the presence of HR-HPV or no HR-HPV.

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Table of Contents

List of Tables

List of Graphs and Figures

Abbreviations

AGC	Atypical Glandular Cells
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-Retroviral Therapy
ASCUS	Atypical Squamous Cells of Undetermined Significance (Bethesda Classification)
AW	Acetowhitening
B-HCG	Beta-human chorionic gonadotropin
BV	Bacterial Vaginosis
CD4	Cluster of Differentiation 4 (T lymphocyte cell)
CDC	Centre for Disease Control
CHBAH	Chris Hani Baragwanath Academic Hospital
CIN	Cervical Intraepithelial Neoplasia
CIS	Carcinoma in situ
CT	Chlamydia trachomatis
HARP	HPV in Africa Research Partnership
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
HR-HPV	High risk Human papillomavirus
HSIL	High grade squamous intra-epithelial lesion
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
IUCD	Intrauterine Contraceptive Device
LBC	Liquid Based Cytology
LEEP	Loop Electrosurgical Excision Procedure
LLETZ	Large Loop Excision of the Transformation Zone
LSIL	Low grade Squamous Intraepithelial lesion
MG	Mycoplasma genitalium
NETZ	Needlepoint Excision of the Transformation Zone

NG	Neisseria gonorrhoea
NHLS	National Health Laboratory Services
NPV	Negative Predictive Value
OC	Oral Contraceptive
Pap smear	Papanicolau smear
PCR	Polymerase chain reaction
PPV	Positive Predictive Value
RCI	Reid Colposcopy Index
ROC	Receiver Operating Characteristic
SA	South Africa
STI	Sexually Transmitted Infection
TPHA	Treponema pallidum haemagglutination assay
TPPA	Treponema pallidum particle agglutination
TV	Trichomonas vaginalis
US	United States
VI	Visual Inspection
VIA	Visual Inspection with Acetic Acid
VILI	Visual Inspection with Lugol's Iodine
VL	Viral Load
WHO	World Health Organization

CHAPTER 1

1.1 Introduction

Cervical cancer is the second most common cancer in South Africa (SA) and the most common cancer in women of reproductive age.[1] Developed countries have brought down the incidence of cervical cancer by implementing screening and treatment of cervical precancerous lesion.[2] SA and other developing countries still have not achieved global screening targets for their population at risk.[3] It is estimated that 54% of the women have been screened in SA in 2013.[4] Poverty, illiteracy, HIV/AIDS have affected prevention programs. Poor infrastructure for diagnosis and treatment of women who have screened positive has further hampered prevention of invasive cervical cancer (ICC) in SA.[5]

The current cervical cancer guideline in SA recommends the use of Papanicolau test (Pap smear) for screening. For the programme to be successful there must be diagnosis and treatment. Diagnosis is by colposcopy followed by biopsy or large loop excision of the transformation zone (LLETZ). LLETZ when combined with the colposcopic examination combines treatment with diagnosis (See and treat).

1.2 Literature Review

Background

Cervical cancer is the second most common cancer in women after breast cancer in SA, while globally it is the third most commonly diagnosed cancer and the fourth leading cause of cancer deaths in females.[1,6] In 2012, 266 000 women died of cervical cancer worldwide and most of these deaths occur in developing countries.[7] The incidence and mortality rates have decreased over the last 40 years in developed countries and this has been attributed to implementation of secondary prevention efforts (effective screening, early diagnosis and treatment for dysplasia and early cancer).[2,3,8]

Cervical cancer is an AIDS defining condition[9] with the relative risk of cervical cancer being ten times higher than in HIV negative women as shown in a large cohort of 16 416 women despite being on anti-retroviral treatment (ART).[10]

Other studies have reported a relative risk for ICC in HIV positive women of between 2-20 times higher than in HIV negative women.[11,12,13] ICC in HIV infected women has been shown to occur at least 10 years earlier than in HIV negative women.[14,15] The prevalence of HIV in SA women as of 2015 is estimated at 18% which is approximately one-fifth of South African women.[16]

Natural History

Human papilloma virus (HPV) is now recognised as a necessary agent in developing cervical cancer.[17,18,19] It is thought that HPV may be integrated into the host genome in some women and will then cause the cells to become dysplastic. HPV is classified into high and low risk according to its association with malignant transformation. High-risk HPV (HR-HPV) (especially type 16 and 18) contributes approximately 50% of high grade cervical lesions.[20]

There is a continuum between HPV infection to CIN1, CIN2, CIN3 and cervical cancer.[21] ICC develops as a result of persistent infection with HR-HPV, commonly acquired through sexual transmission.[17] HIV seropositive individuals have a higher incidence of premalignant lesions especially if there is HPV coinfection, potentially increasing the likelihood of low grade squamous intraepithelial lesion (LSIL) progressing to high grade squamous intraepithelial lesion (HSIL).[22]

The long natural history of CIN is important and allows for the treatment of premalignant lesions. The description of the natural history according to IARC is shown in table 1.1.[23]

Table 1.1 The natural history of SIL

Baseline cytology	Regression at 24 months	Progression to HSIL at 24 months	Progression to invasive cancer
ASCUS	68.2%	7.1%	0.3%
LSIL	47.4%	20.8%	0.2%
HSIL	35.0%	23.4% (persistence)	1.4%

The rates of regression are lower as the severity of lesion increases. A 40 year review of literature in the United States (US) by Ostör reported a regression of CIN 1 (LSIL) to be 60%, progression to CIN 3 (HSIL) to be 10% and progression to invasion 1%.[24] The same study found that CIN 3 had a regression likelihood of 33% and progression rate to invasion was estimated to be 12%.

McCredie et al. conducted a retrospective review where a group of 143 women with CIN 3 who received close follow up and no treatment were compared with 593 women who had treatment.[25] There was a 64% persistence of CIN 3 at 6 and 24 months in 143 women with a cumulative incidence of ICC reported to be 31.3% (95% CI 22.7-42.3) at 30 years and 50.3% (95% CI 37.3-64.9) in 92 of women who had disease persistence within 50 years. However in the treated 593 women the cancer risk was 0.7%. This confirms that women not followed up and treated for CIN 3 are at high risk for developing cervical cancer. Treatment of cervical intra-epithelial neoplasia (CIN) will result in the reduction of cervical cancer by 90%.[26]

Screening

Screening is the use of methods to detect unrecognized health risks or diseases in order to permit timely intervention. The success in the prevention of cervical cancer has been attributed to the conventional Pap smear. Liquid Based Cytology (LBC) is newer and more expensive to perform than the conventional Pap smear.[7,27] In addition it has benefits for using residual cellular material for molecular testing of agents such as Chlamydia trachomatis (CT) or HPV. However, in a randomised controlled trial performed within the Dutch national cervical screening program LBC did not perform better than conventional Pap smear in terms of relative sensitivity and positive predictive value for detection of cervical cancer precursor lesions.[28]

SA implemented a cytology based national cervical cancer screening programme in 2001, with a plan to achieve a coverage of 70% of women in the first 10 years of its inception.[29] The uptake for cervical cancer screening in SA is low and was estimated to be 54% in 2013.[4] A number of intrapersonal, socioeconomic and institutional barriers have been identified as the cause of this low uptake; this includes the expected feeling of pain, anxiety from pelvic examination, limited access to transportation and its cost, health care facilities, shortage of trained staff and long waiting times among other things.[30,31,32]

Because this type of screening programme is cytology based, it comes with major logistical and programmatic challenges. It requires laboratories with well-trained cytotechnologists, pathologists who can process and report the specimens; good quality control; a system that can communicate the results to the women and colposcopists who will further diagnose and manage the women with abnormal findings.[33] This then will require the women to follow up their results, resulting in a risk for loss to follow up as accessibility to these facilities tends to be challenging. Despite these challenges, the Pap smear has been shown to reduce cervical cancer incidence and mortality in large populations in developed countries.[33]

Visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) are alternative screening methods, deemed to be simple and inexpensive, moreover they are components of the RCI (Table 1.2). The World Health Organization (WHO) recommends the use of VIA/VILI as screening methods in low-and middle-income countries in the context of screen and treat, as this is associated with reduced loss to follow up.[7] In VIA, 3-5% of acetic acid is applied to the cervix and it is then visualized to see if there are any changes. Pre-cancerous lesions turn white (acetowhitening) due to the high intracellular protein content, which is classified as positive VIA. VILI involves the staining of the cervix with Lugol's iodine and because normal squamous cells contain glycogen, they will stain brown while abnormal cells will not take up the iodine and will be classified as positive VILI. These can be viewed by a naked eye or through colposcopy. Abnormal or suspicious areas can be biopsied or be treated immediately.

HPV DNA screening has also been proposed as an alternative secondary screening method and has been added in the new (2017) South African cervical screening guidelines.[34,35] A randomised controlled trial in India shows that screening by HPV DNA testing allows for earlier detection of CIN 2-3 and therefore is highly effective in prevention of ICC.[36] HPV testing alone has a high sensitivity and a low in specificity at detecting CIN 2-3.[37]

Meta-analyses show that a combination of cytology and HPV DNA testing is a more cost-effective approach than conventional cytology alone as a screening tool for cervical cancer.[37,38] The challenges with HPV DNA testing in developing countries is the high cost, the fact that it is time consuming and that it requires sophisticated laboratory infrastructure amongst other things.[39] Newer alternatives like the CareHPV test have been introduced in

the market and have been shown to perform well in low-resource settings.[40] This test is a rapid test which detects 14 HR-HPV types and has a sensitivity and specificity of 88% and 85% respectively for CIN 2+.[40]

HPV testing is not recommended in patients below the age of 30 years, because HPV infection is very high among the younger age groups resulting in a decreased specificity.[41] The prevalence of HPV in HIV infected women is five times higher. The chance of persistence and progression is higher, warranting more intensive surveillance and a low threshold for treatment in these women.[42]

Colposcopy

Colposcopy involves the examination of the cervix using a binocular microscope which allows a magnification of 6-40 times. The examination of the cervix is important for visualizing the entire transformation zone and the lesion in order to plan management. Traditionally, the lesion was biopsied and treatment was based on histology. With see and treat clinics treatment is carried out at the first visit.

Screening with various methods have different sensitivity and specificity and colposcopy is therefore an important modality in increasing sensitivity and increasing specificity. The sensitivity of VIA has been reported to be 50%-76% and specificity of 51%-92%.[30] The sensitivity and specificity for VILI has been reported to range between 76%-97% and 73%-91% respectively in a multicentre study in Africa and India involving 54 981 women.[43] In a recent meta-analysis by Mustafa et al. the sensitivity and specificity of the conventional Pap smear was reported to be 70-84% and 88-95%.[44] The sensitivity and specificity of HPV testing in a meta-analysis of eight studies with a total number of 7872 participants, ranged from 77%-96% and 32%-82% respectively.[30]

The importance of having an accurate colposcopy diagnosis in order to reduce overtreatment cannot be over emphasized. Colposcopic assessment is subjective with a high likelihood of inter-observer variability especially when interpreting abnormal features.[45] The accuracy of colposcopy is dependent on age, antecedent Pap smear, size of the lesion and the presence of HR-HPV amongst other things.[46,47]

In addition, the accuracy of colposcopy seems to be increased as the severity of the lesion increases. The accuracy is further improved by performing multiple colposcopically directed biopsies of the lesion.[48,49] A large retrospective series including 84 244 women demonstrated that cases with HSIL or malignancy on colposcopic impression had histology confirming the colposcopic finding in 85% of the cases, while in the remaining 15% of cases histology revealed either benign or LSIL.[50] Muwonge et al. further demonstrated that colposcopy detected 95% of CIN≥2 confirmed by histology in a meta-analysis looking at the performance of colposcopy in sub-Saharan African countries.[51]

The accuracy of colposcopy in HIV seropositive women has been a concern as these women are younger and often desire fertility. A multicentre cohort representing a total of 2024 women of which 1618 were HIV seropositive, found that the sensitivity of a colposcopic impression of high grade disease for a high grade biopsy result was only 29%, PPV of 26%, specificity and NPV higher at 96% respectively.[52] In the same study, women with abnormal cytology were more likely to have abnormal colposcopy findings compared to their seronegative counterparts.[52] Another multicenter international study among HIV seropositive women demonstrated that a low-grade colposcopic impression had sensitivity of 98%, specificity of 63% with a PPV of 22%.[53] In contrast, Branca et al. reported different findings to the previously mentioned studies with 79% sensitivity and 75% specificity for colposcopy impression in HIV positive women.[54] Variations in colposcopic skills and differences in lesion size have been reported as some of the reasons for these disparities.

Colposcopy performs poorly as a primary screening tool, it is not very accurate and it increases the risk of overtreatment in patients when used alone for screening.[55] Although subjective, colposcopic impression has been shown to improve with further training and certification of colposcopists and appropriate quality control tools. In a meta-analysis where the end point was CIN 2-3 in women who screened positive, the pooled sensitivity and specificity of the colposcopic performance was reported to be 95% (95% CI: 86 - 98) and 42% (95% CI: 26 - 61) respectively.[44]

Different scoring systems have been developed in order to increase its accuracy. One of the scores called the Reid colposcopy index (RCI) was proposed by Reid and Scalzi in 1985.[56] This method predicts the histological diagnosis on the basis of four colposcopic features which includes the colour of acetowhitening, margins, vessels and iodine staining. Each parameter is scored from 0 to 2 and then the scores added to give a total score. A total score of 0 to 2 points is likely to be CIN 1; 3 to 4 points is an overlapping lesion: likely to be CIN 1-2; 5 to 8 points likely to be CIN 2-3 lesions. Table 1.2 explains the allocation of points for every colposcopic sign. A modified version of the RCI has iodine testing omitted as a parameter.

The RCI is the most widely used scoring system and has been shown to be of good value in diagnosing premalignant lesions.[49] The original study in which Reid and Scalzi prospectively recorded colposcopic features in 72 women and correlated with histologic findings, found that the predictive accuracy of the individual parameters was independent of each other, however combining these four individual signs into a colposcopic index was 97% correct in predicting histological diagnosis.[56]

Other studies have shown a sensitivity of between 74% to 94%, a specificity of 90% to 99.6% a PPV of 80.9% to 95.8% and a NPV of between 70% to 98.3% using a score of 5 and an endpoint of >CIN1.[57,58,59] However when a cut-off of 4 was used, a study from India showed sensitivity of 100% and specificity of 88.3%.[59]

In contrast, Ferris et al.[60] colposcopically examined 3549 women from the US, found that the RCI had a poor sensitivity (37.3%) for detecting CIN 2 or above. The most notable limitation from this study was the omission of Lugol's iodine stain testing.

Table 1.2 The Reid Colposcopy Index [56]

Colposcopic Signs	0 Point	1 Point	2 Points
Colour of acetowhite (AW) area	Low intensity acetowhitening, snow-white, shiny AW, indistinct AW, transparent AW, AW beyond the transformation zone	Grey-white AW with shiny surface	Dull, oyster-white, Grey
AW lesion, margin and surface configuration	Feathered margins, angular, jagged lesions, flat lesions with indistinct margins, microcondylomatous or micro papillary surface	Regular lesions with smooth, straight outlines	Rolled, peeling edges, internal demarcations (a central area of high-grade change and peripheral area of low-grade change)
Vessels	Fine/uniform vessels, poorly formed patterns of fine punctations and or fine mosaic, vessels beyond the margin of the transformation zone; fine vessels within microcondylomatous or micro papillary lesions	Absent vessels	Well defined coarse punctuation or coarse mosaic
Iodine staining	Positive iodine uptake giving mahogany brown colour, negative uptake of lesions scoring 3 points or less on the above three categories	Partial iodine uptake by a lesion scoring – or more points on above three categories – variegated, speckled appearance	Negative iodine uptake by a lesion scoring 4 or more points on the above three criteria

Strander et al. developed another scoring system called the Swede score as depicted in table 1.3.[61] This score includes lesion size as an additional parameter to the four RCI parameters illustrated in table 1.2.

The same study demonstrated specificity of 90% for a Swede score of ≥8 and a score of ≤5 was more likely to have histology that is <CIN2.[61] Other studies have shown sensitivity of between 36.8% to 38% and a specificity of between 95% to 100% for a Swede score of ≥8.[59,62]

When the Swede score was lowered to 5 the sensitivity was reported to range between 65% and 100% and sensitivity of between 82% and 91.3%.[59,62] Studies support the see and treat method in low resource settings when the Swede score is 8 or higher due to the high specificity for ≥CIN2.[59,61,62,63] The Swede score has also been found to be a useful tool in reducing the need for diagnostic biopsies when evaluating atypical cervical cytology in pregnant women with a specificity for HSIL of 52.9% using a score of 5.[64]

Table 1.3 Swede Score[61]

Colposcopic signs	**0**	**1**	**2**	**Score**
Acetouptake	None or transparent	Shady, milky (not transparent)	Distinct, opaque white	
Margins / Surface	Diffuse	Sharp but irregular, jagged, "geographical" satellites	Sharp and even, difference in surface level including "cuffing"	
Vessels	Fine, regular	Absent	Coarse or atypical	
Lesion size	<5mm	5-15mm or 2quadrants	>15mm or 3-4 quadrants or endocervically undefined	
Iodine Staining	Brown	Faintly or patchy yellow	Distinct yellow	

The International Federation for Cervical Pathology and Colposcopy (IFCPC) in 2011 developed the IFCPC scoring system.[65] The main aim was to standardize interpretation of the colposcopic findings and organize comprehensive classification. However this scoring system is not used as much as the RCI and the Swede score. In this assessment, a general assessment is first made which involves adequacy or inadequacy of the transformation zone. Secondly, a colposcopic description of the transformation zone is made (original squamous epithelium, columnar epithelium, metaplastic change, location and size of lesion). This is a description of whether the transformation zone is in the endocervix, ectocervix or between the two areas. This allows the colposcopist to plan the management. Thirdly, a description of acetowhiteness and vascular changes is made. Finally, the colposcopist gives a colposcopy diagnosis

which may be normal, LSIL or HSIL. Clinically it is important to describe adequacy of the TZ because it directs treatment.

There has not been many studies that compare the RCI and Swede colposcopy scoring systems, however when compared to each other both scores perform very well according to literature. The addition of the lesion size on the Swede score has been shown to have an additional advantage in aiding and assessing the feasibility of treatment modalities according to an Indian prospective study.[66] Similar findings were also noted in a recent study conducted in India.[59] Based on the aforementioned findings the Swede score seems to be a preferred scoring method. When comparing the individual parameters, acetowhiteness has been shown by a number of studies to be the most sensitive parameter in predicting CIN 2-3.[61,67,68]

The table below compares those studies which compared scoring systems and where the Reid and the Swede scores were included. The IFCPC was also compared in two of the studies where the sensitivity was 79.1% and was 63.6% in the Li and Carreiro study. The score that was used as a cut-off to determine the parameters shown in the table was only known in three studies studies.[59,66,70]

Table 1.4 Comparison of performance of Reid, Swede and IFCPC scores in various studies

Study, year,(Country), N	Sensitivity	Specificity	PPV	NPV
Carreiro, 1990[69] (Italy) n= 134				
Reid	85.3%	93.9%	93.5%	86.1%
International Classification	75.0%	90.9%	89.4%	77.9%
Li, 2017[70] (China) n= 525				
Reid (cut-off of ≥5)	38.3%	95.5%	66.6%	86.9%
Swede (cut-off of ≥8)	13.1%	98.5%	68.4%	83.0%
IFCPC	63.6%	96.0%	78.7%	91.9%
Ranga, 2017[66] (India) n= 150				
Reid (cut-off of ≥5)	96.9%	95.3%	88.8%	98.8%
Swede (cut-off of ≥5)	100%	88.3%	76.7%	100%
Kushwar, 2017[59] (India) n= 80				
Reid (cut-off of ≥5)	94.4%	91.4%	80.9%	97.7%
Swede (cut-off of ≥5)	100%	91.3%	82.6%	100%

Treatment

Treatment of CIN may be by cryotherapy, large loop excision of the transformation zone (LLETZ), laser ablation, laser conisation, cold knife conisation and hysterectomy. A Cochrane meta-analysis on treatment of CIN revealed that there is no difference in efficacy of eradicating CIN among the excisional (laser conisation, LLETZ, loop electrosurgical excision procedure [LEEP], needlepoint excision of the transformation zone [NETZ]) and destructive (electrocoagulation, cryotherapy, laser ablation) conservative treatment methods.[71] In 'see and treat' clinics treatment is mainly with LLETZ or cryotherapy. The advantage of LLETZ is that it

provides a specimen for histology. Cryotherapy can only be used if the lesion is completely visible and if the lesion is present in less than three quadrants.

The benefits of the 'see and treat' clinics are that women get treated immediately, which results in the reduction of patient loss to follow-up.[9, 71] Traditionally treatment was based on obtaining histological diagnosis with a punch biopsy and then treating at a 2nd visit. The accuracy of punch biopsies have been shown to be poor with only 50% of the lesions diagnosed, but increasing the number of biopsies has been shown to increase the sensitivity of colposcopy.[48,49,72,73] An additional 37% increase in detection of CIN2 was shown when random biopsies were taken in a study by Pretorius.[72]

'See and treat' clinics with treatment based on colposcopy may lead to overtreatment or under treatment. The quoted overtreatment rate in a South African Tertiary Institution was 6.7 - 8.9% with an international quoted rate of between 13.3 - 83.3%.[74,75] A meta-analysis representing 4611 women justifies the see and treat method especially in women with a HSIL Pap smear and a high grade colposcopic impression, with the overtreatment rate found to be 11.6%.[76] This is lower than the quoted international overtreatment rate.

There are no colposcopic features that diagnose micro-invasive disease however when features at colposcopy suggest a lesion is more severe than CIN 3 then it is better to do a LLETZ or cone biopsy. Colposcopic directed punch biopsies have been shown to under diagnose micro-invasive disease when compared to excisional biopsies performed by knife or loop excision, particularly if high grade disease is present.[77,78]

Treatment is associated with complications classified as immediate and late. The immediate complications include bleeding and infection with an incidence of 2-10% and 0-2% respectively.[79,80] Uterine perforation, bladder and rectal injury are also classified as immediate, however they are very rare.[81]

Late complications include cervical stenosis and cervical insufficiency with an incidence ranging between 4 to 8 percent among the different methods of treatment.[82] A systematic review of randomized trials of conisation for CIN found no significant difference in the rate of haemorrhage or CIN recurrence among the three techniques (cold knife, laser, LLETZ).[83]

WHO does not recommend hysterectomy as treatment for pre-cancerous lesions, however it may be used in women with other gynaecological problems.[7]

1.3 Problem Statement

In SA, women are referred to colposcopy with recurrent LSIL, recurrent atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells (AGC), HSIL and more severe lesions. HIV infected women are referred with any abnormal Pap smear. The new cervical cancer screening guidelines now recommend Pap smear at the diagnosis of HIV in women who are HIV infected. Persistence of cervical cancer precursor lesions is high in HIV infected women. These women will continue to present the colposcopist with a challenge regarding immediate treatment or treatment based on punch biopsy.

In a meta-analysis of colposcopy, the pooled sensitivity and specificity are reported to be 95% (95% CI: 86 - 98) and 42% (95% CI: 26 - 61).[44] This study considered any colposcopic assessment and did not evaluate the accuracy of any particular scoring system. A study done at the colposcopy clinic at Chris Hani Baragwanath Academic Hospital (CHBAH) found that normal histology was found in 1.3% of patients, and CIN 1 or HPV in 8.4% in 922 women treated in a "see and treat" approach.[74] The concern with a see and treat approach is that women may be over treated. The colposcopic assessment was based on the Reid colposcopic index.

Colposcopists in SA are not trained in a uniform manner. Most colposcopists in SA record their findings using some of the recommended colposcopic changes. Experts have recommended standardized representations of colposcopic findings in a drawing, using symbolic and scoring methods such as the RCI and Swede score.[56,62] The performance of colposcopy using a score has not been evaluated in HIV infected women.

The purpose of the HARP study was to improve cervical cancer prevention programmes for HIV infected women in Africa, by evaluating the effectiveness and cost-effectiveness of alternative screening strategies and by developing algorithms leading to earlier detection and management of cervical cancer in these high-risk populations. In the study women with any positive cervical cancer screen had a colposcopic assessment using the Swede score and a

colposcopic directed biopsy was performed to obtain histology. This study therefore provided the opportunity of assessing the accuracy of the scoring systems in colposcopic diagnosis in HIV infected women.

Justification for the study:

HIV infected women are referred with less severe abnormalities than HIV negative women and may therefore be at a greater risk of over-treatment in see and treat programme. However in a programme where a punch biopsy is performed prior to treatment may lead to loss to follow up and risk of under-treatment. The accuracy of colposcopy is therefore important.

1.4 General Objectives

To determine the accuracy of diagnosis of CIN at colposcopy using either the Swede score or the Reid Colposcopy Index in African HIV infected women.

1.5 Specific Objectives

1. To describe the cytological abnormalities on Pap smear, HPV findings, VIA and VILI findings.
2. To describe the histology obtained with punch biopsies.
3. To determine the performance of the RCI (sensitivity, specificity, NPV and PPV).
4. To determine the performance of the Swede score (sensitivity, specificity, NPV and PPV).
5. To compare the performance of the Swede score and RCI.
6. To compare the performance of the Swede score in women with equivocal Pap smear results (ASCUS/ LSIL) versus women with HSIL.
7. To compare the performance of the RCI in women with equivocal Pap smear results (ASCUS/ LSIL) versus women with HSIL.

CHAPTER 2

2.1 Methodology

2.1.1 Study Setting

The South African arm of the HARP study was conducted at the Hillbrow Community Health Centre (CHC) and subjects were recruited from this site and surrounding primary health care clinics. Hillbrow is a suburb which is located in central Johannesburg, Gauteng province in SA. It is known for its high population density, unemployment rates and crime. The majority of residents are migrants from townships, rural areas of SA and other African countries, living in poverty.[84] In 2011 the area had a total population of just under 75 000 with mainly people who are black African, with the coloured race making up the second most common race.[84]

2.1.2 Study Population

This study is a secondary data analysis using the data collected for the HARP study at the South African site. The HARP study has been described previously[85], but briefly the women were recruited from HIV treatment centres and surrounding primary health care clinics in Hillbrow. The eligibility criteria included women between the ages of 25-50 years, HIV-1 positive, not pregnant or more than 8 weeks post-partum, resides in Johannesburg and be willing to undergo the study procedures and its follow up. It was a cohort study conducted over 18 to 24 months from November 2010 to April 2014. HIV testing was done using locally-validated serological rapid assays. A positive test was followed by use of a type-discriminating test (SD Bioline, ImmunoComb II and Biospot). In case of uncertainty, a third ELISA or Western Blot assays was used.

Women who were already on the clinics' database and known to be HIV positive were not required to submit record of the HIV status. Consent was obtained and eligibility checked in HIV positive women. Women were tested for pregnancy at the centre upon arrival before they were included in the study group. They had to have been using some form of effective contraception, defined as a method that reliably prevents pregnancy, whether hormonal or barrier.

Exclusion criteria:

1) HIV-negative or HIV-2 positive only.

2) Ages <25 or >50 years.

3) Women who had a total hysterectomy or history of cervical cancer treatment.

4) Physical or mental inability to undergo routine cervical cancer screening or unable to provide informed consent.

5) Pregnant or less than 8 weeks post-partum; and

6) Unwillingness to sign consent forms.

This study used the baseline data from all women recruited in the SA arm of the HARP study the exclusion and inclusion criteria was the same, but only data of women from the SA arm of the study and who had had a biopsy was used in this study.

2.1.3 Study Procedures

Nurse practitioners administered questionnaires to obtain socio-demographic information and sexual history in the original HARP study. Women had a clinical examination, a conventional Pap smear, VIA, VILI, and a vaginal lavage for HPV testing. VIA was performed using 3-5% acetic acid. Followed by a schillers test using Lugol's iodine. Any women who had any screening test that was positive was referred to colposcopy.

Colposcopy was performed by trained Colposcopists (Medical Officers or Gynaecologists) using digital colposcopy. The patient was placed in lithotomy, a speculum was inserted and the saline technique was used for the colposcopy. The angio-architecture was examined, followed with the application of 3-5% acetic acid and then Schillers test was performed using Lugol's iodine. A four quadrant biopsy (using a Tischler's forceps) and a directed biopsy (if a lesion was present) was performed and sent to the laboratory in 10% formalin.
Women with CIN 2/CIN3 were referred to a treatment centre for further management. Management of these women was according to the SA guidelines. The biopsy specimens were sent to the same laboratory and were interpreted using the CIN classification.

The table below explains the other tests that were performed. Other sexually transmitted infections were tested using Ecto+endocervical (Dacron) swab collection and polymerase

chain reaction (PCR) test performed for NG, CT, Trichomonas vaginalis (TV) and Mycoplasma genitalium (MG).

Table 2.1 Tests performed

Test performed	Name of test
CD4 (cells/ mm)	FACS count, Becton-Dickinson, NJ
Plasma HIV viral load	Roche Taqman technique.
Syphilis serology	Rapid plasma reagin (RPR).
HPV genotyping	Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp)
Cytology	Conventional Pap smears - these were sent to the NHLS and reported in accordance with the Bethesda System. The NHLS has strict internal and external quality controls.

The current study used all the data collected using the procedures above.

2.1.4 Study Design

This study was conducted as a cross sectional study using a secondary data analysis. The baseline data collected during the South African arm of the HARP study was used.

2.1.5 Data Management

Data for this current study was extracted on the 25th of November 2016 from the HARP study database. The following variables were extracted and used: age, race, parity, smoking, contraception use, ART use, Pap smear, VIA/VILI, HR-HPV, colposcopy findings, Swede scores and histology findings.

2.1.6 Sample size

A sample size was not calculated, we used all the data that was available from the SA arm of the HARP study. Studies of comparisons between different colposcopy scores had between 80 - 525 patients.[59,66,69,70]

2.1.7 Data Analysis

Categorical variables were described using frequencies and percentages and continuous variables were described using means (SD) and medians (IQR with ranges) in the current study. A new histology outcome variable was made for histology of CIN2 and more severe as this is

the histology which is the threshold for treatment. The Reid score was not recorded separately in this study so it was imputed using the 4 parameters within the Swede score. The variables acetowhiteness, Iodine uptake, vascular changes and margin status were reported separately in the study and were used to create the Reid Score. New variables for each of the scores (Reid and Swede), were made to reflect each breakpoint of the scores for determining the sensitivity, specificity, positive predictive value and negative predictive value.

A Swede score/Reid score would compare the score below and above using the score as a breakpoint. For example, the sensitivity and specificity of a score of 6 would be all the women with a score of 5 and below compared to all the women with a score of 6 and more. Receiver Operating Characteristic (ROC) curves were used to graphically illustrate the performance of the 2 scores across the antecedent Pap smear category. The comparison was made using a chi^2 test. It was possible to use ROC curves as the scores were considered ordinal and not categorical.

2.2 Ethics

The original study received ethical approval from the Ministry of Health in Burkina Faso (no. 2012-12-089), University of the Witwatersrand (M110707) and the London School of Hygiene and Tropical Medicine (no. 7400). This study was approved by the University of Witwatersrand's Ethics committee (study number M161126) (Appendix D). Permission to use data from the South African arm of the HARP study was requested from the HARP Study Group in conjunction with the South African HARP co-ordinators and permission was granted after a concept paper (Appendix B) was presented to the HARP Study Group. A letter from the South African HARP study group co-ordinators was also granted (Appendix C). No consent was obtained from the subjects as this was a secondary data analysis.

2.3 Funding

The original HARP study was funded by the European Union Seventh Framework Programme. The current study was self-funded by the Researcher and funds were used only for stationery.

CHAPTER 3

3.1 Results

3.1.1 Study Population and Exclusions

A total of 2361 women were screened from the South African arm of the HARP study and only a 624 were eligible and included in the study. A total of 577 women were included in the final study. The 47 (7.53%) women excluded and reasons thereof are illustrated in figure 3.1.

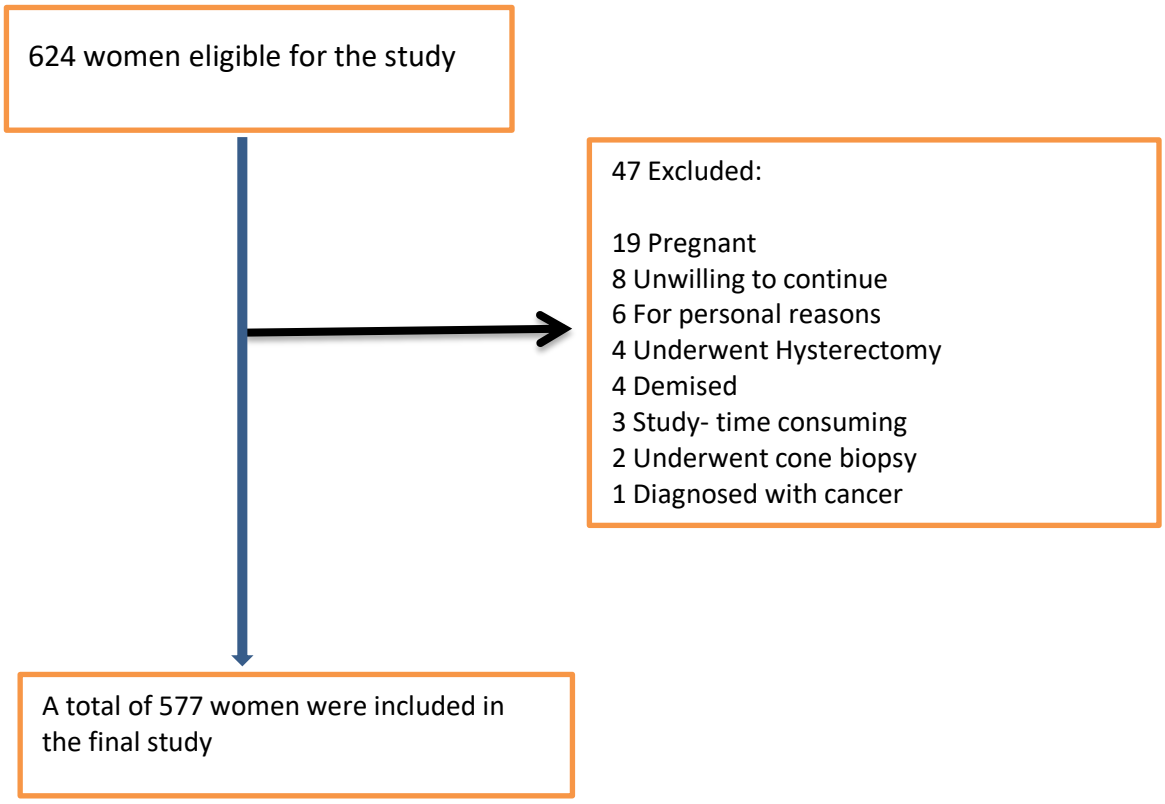

Figure 3.1 Flow diagram showing the reasons for withdrawal from the study

3.1.2 Demographics

3.1.2.1 Age, Race and Nationality

The mean age was 34 (SD±5.89) with a range of 25-50 years. Most of the participants were Black. There were 412 (71.40%) women of South African origin. The remaining 165 (28.60%) women were non-South African.

3.1.2.2 Socio-economic status

There were 319 (55.29%) women who were employed and 258 (44.71%) were unemployed. Of the employed group, the mean monthly income was R2476.47 (SD±R2825.78). The majority of the women had some form of formal education and only 6 (1.04%) had no formal education at all.

3.1.2.3 Parity, contraception and sexual history

Most women (n=547, 94.8%) had previously been pregnant. The median number of pregnancies was 2 (IQR= 1.00-3.00; range= 1-13). Sixty four percent (n=368) of the women were not using any contraception, 207 (36%) were using an effective modern contraceptive.
The median age of sexual debut was 18 years (IQR= 16-19; range= 13-25).
There were 154 (26.69%) women who had a history of a previous or current active sexually transmitted infection. Evidence of the following infections was found; Trichomonas vaginalis in 94 (16%) women, Mycoplasma genitalium in 44 (8%) women, Chlamydia trachomatis in 27 (5%) women, Neisseria gonorrhoea in 11 (2%) women, Treponema pallidum in 9 (1.5%) women and Herpes simplex in 546 (95%) women.

3.1.3 Smoking

There were 508 (88.04%) women who never smoked cigarettes, 38 (6.59%) previously smoked but stopped and 31 (5.37%) were still smoking.

3.1.4 HIV status

The mean age at diagnosis was 29 years (SD±29.9) with range from 17-46 years. The partner's HIV status was negative in 106 (22.94%) women, positive in 179 (38.74%) and in 177 (38.31%) the women did not know their partner's status.
The baseline CD4 count was ≥ 500 cells/mm^3 in 210 (36.40%) women, was between 350 and 499 cells/mm^3 in 176 (30.50%) women, between 200-249 cells/mm^3 in 140 (24.26%) women and ≤ 200 cells/mm^3 in 51 (8.84%) women. The median CD4 count was 427 cells/mm^3 (IQR = 323 – 579) and the range 45 to 1140 cells/mm^3.
The median plasma viral load was 552.50 copies/ml (IQR = 44.00 – 10918.50); range 40 to 581 000 copies/ml. WHO clinical stages was as follows; 486 (84.23%) were clinical stage 1,

23 women (3.99%) were stage 2, 67 (11.61%) women were stage 3 and 1 (0.17%) woman was stage 4.There were 370 (64.12%) women who were on ART and the ART use according to CD4 count is shown in table 3.1.

Table 3.1 Description for the use of ART.

ART USE	Frequency (n)	Percentage (%)
On ART	370	64.12
Not on ART (CD4<350 cells/mm^3)	50	8.67
Not on ART (CD4>350 cells/mm^3)	157	27.21
Total	577	100.00

3.1.5 Cytology

There were no Pap smears with any cytology suggestive of invasion. The results of the Pap smears are reflected in Figure 3.2.

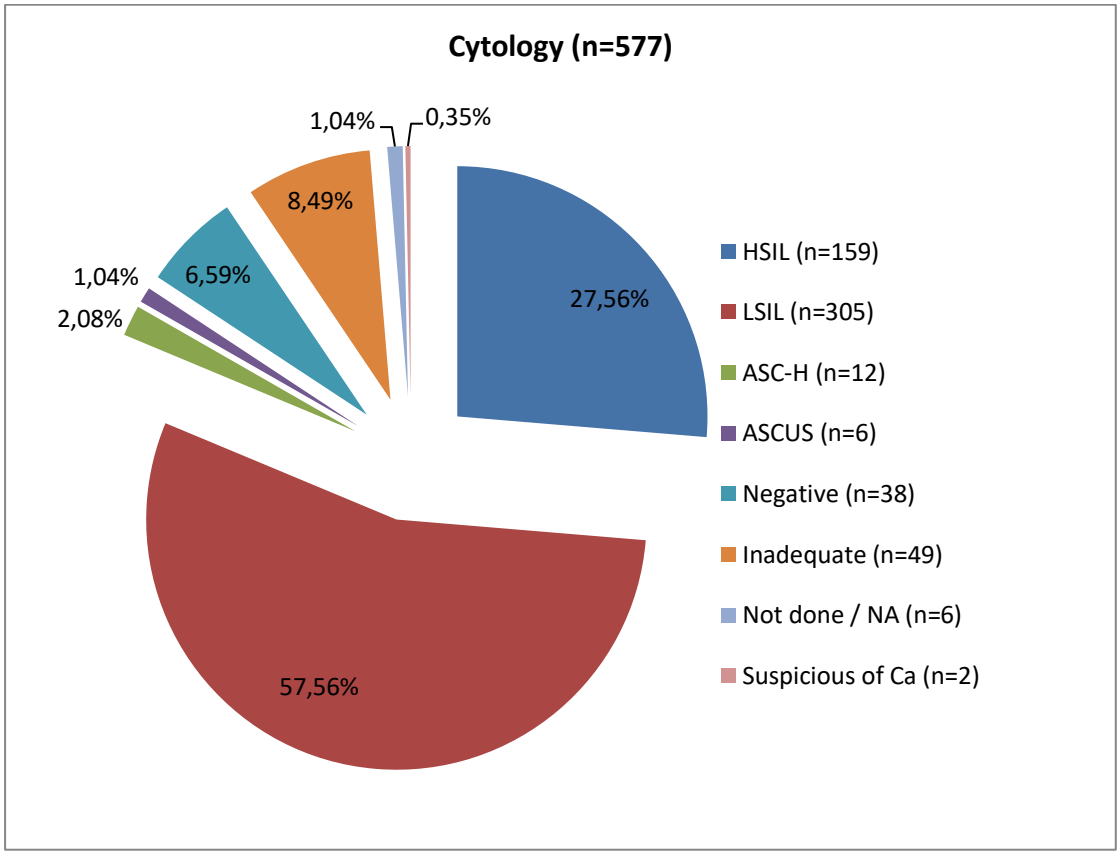

Figure 3.2 Representation of cytology findings

3.1.6 High Risk Human Papilloma Virus (HR-HPV)

HR-HPV was found to be positive in 374 (64.82%) women. A total of 106 (28.60%) women tested positive for a single strain of HR-HPV and 268 (36.22%) had multiple types. The number of multiple types ranges from 2 to 20.

3.1.7 VIA and VILI

VIA was positive in 162 women (28.08%) and there were 219 (37.95%) women with a positive VILI test result.

3.1.8 Histology

Table 3.2 is a representation of the overall histology illustrating that 129/577 (22.36%) women had CIN ≥ 2.

Table 3.2 Overall Histology results

CIN	Frequency (n)	Percentage (%)
Normal	33	5.72
HPV	230	39.86
CIN 1	185	32.06
CIN 2	76	13.17
CIN 3	53	9.19
TOTAL	577	100.00

*<CIN 1 could be completely normal or HPV

3.1.9 Comparison of Reid RCI and Swede Scores

Table 3.3 shows the proportion of women for the different scores with the Reid score.

Table 3.3 A description of the proportion of the different scores using the RCI.

Total RCI Score	Frequency (n)	Percentage (%)
0	71	12.33
1	106	18.40
2	90	15.62
3	79	13.72
4	72	12.50
5	59	10.24
6	52	9.03
7	29	5.03
8	18	3.12
Total	576	100.00

Table 3.4 shows the proportion of women with different scores when using the Swede score

Table 3.4 A description the proportion of the different scores using the Swede Score

Total Swede Score	Frequency (n)	Percentage (%)
0	70	12.15
1	101	17.53
2	67	11.63
3	58	10.07
4	61	10.59
5	55	9.55
6	47	8.16
7	53	9.20
8	28	4.86
9	21	3.65
10	15	2.60
Total	576	100.00

Below is the Receiver Operating Characteristic (ROC) curve illustrating the prediction of CIN 2 lesions and above for the Swede score. It also illustrates that a score of 5 has the best sensitivity without much reduction in its specificity.

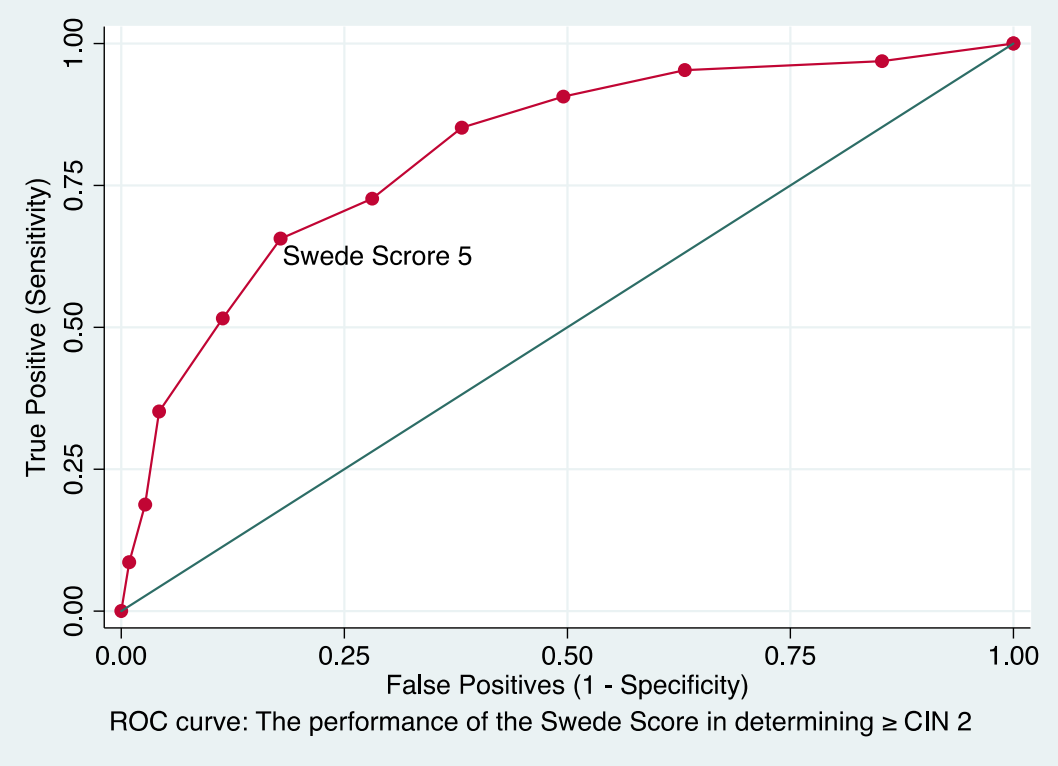

Figure 3.3 ROC graph for predicting ≥ CIN2 using the Swede Score (AUC=0.81)

Table 3.5 below gives the sensitivity, specificity, PPV and NPV and mirrors the ROC curve. It illustrates that a Swede score less than 5 would increase the sensitivity but would reduce the specificity. In a see and treat clinic this will mean over-treating more women than necessary.

Table 3.5 Swede score sensitivity, specificity, PPV and NPV

Swede Score- using a cut-off score of	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive Value (95%CI)	Negative predictive value (95%CI)
Score 1 (n=507)	96.90% (92.30% - 99.10%)	14.70% (11.60% -18.40%)	24.70% (21.00% - 28.60%)	94.30% (86.00% - 98.40%)
Score 2 (n=406)	95.30% (90.20% - 98.30%)	36.80% (32.40% - 41.50%)	30.30% (25.90% - 35.00%)	96.50% (92.50% - 98.70%)
Score 3 (n=339)	90.70% (84.30% - 95.10%)	50.40% (45.70% - 55.20%)	34.50% (29.50% - 39.80%)	95.00% (91.40% - 97.40%)
Score 4 (n=281)	85.30% (78.00% - 90.90%)	61.80% (57.20% - 66.30%)	39.10% (33.40% - 45.10%)	93.60% (90.20% - 96.10%)
Score 5 (n=220)	72.90% (64.30% - 80.30%)	71.90% (67.50% - 76.00%)	42.70% (36.10% - 49.60%)	90.20% (86.60% - 93.10%)
Score 6 (n=164)	65.10% (56.20% - 73.30%)	82.10% (78.30% - 85.60%)	51.20% (43.30% - 59.10%)	89.10% (85.70% - 91.90%)
Score 7(n=118)	51.90% (43.00% - 60.80%)	88.60% (85.30% - 91.40%)	56.80% (47.30% - 65.90%)	86.50% (83.00% - 89.50%)
Score 8 (n=64)	34.90% (26.70% - 43.80%)	95.80% (93.50% - 97.40%)	70.30% (57.60% - 81.10%)	83.60% (80.10% - 86.70%)
Score 9 (n=36)	18.60% (12.30% - 26.40%)	97.30% (95.40% - 98.60%)	66.70% (49.00% - 81.40%)	80.60% (77.00% - 83.80%)
Score of 10 (n=15)	8.50% (4.30% - 14.70%)	99.10% (97.70% - 99.80%)	73.30% (44.90% - 92.20%)	79.00% (75.40% - 82.30%)

Below is a ROC of the Reid score in predicting CIN 2 and above.

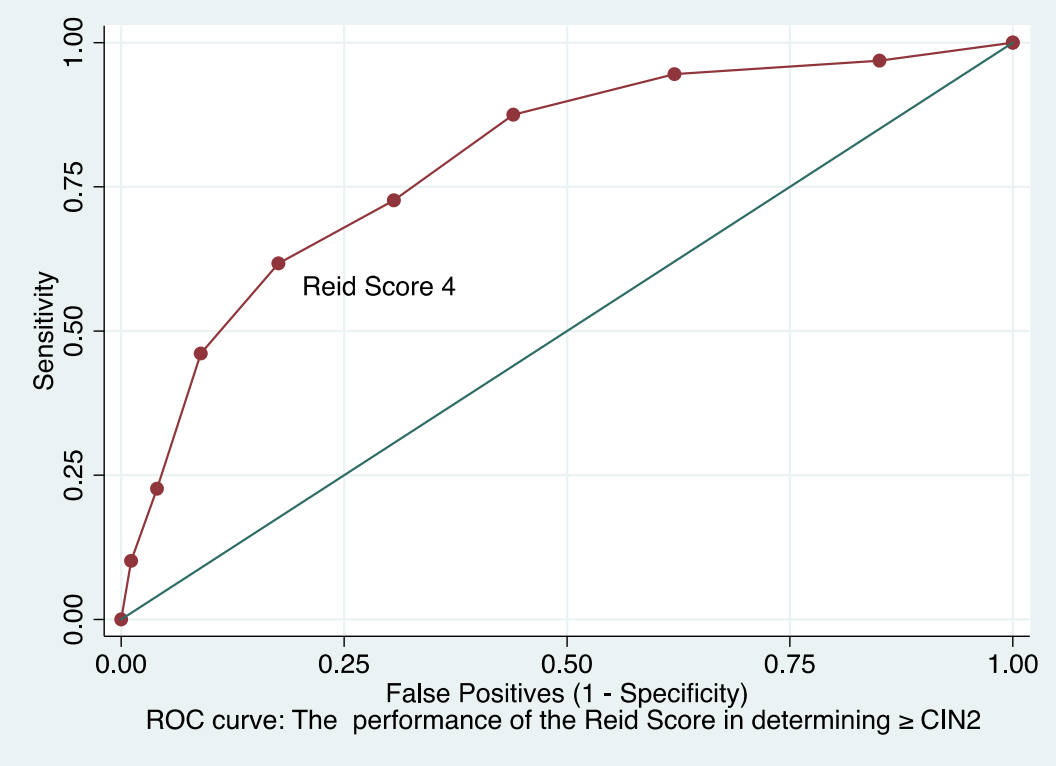

Figure 3.4 ROC graph of Reid score predicting ≥ CIN 2 (AUC=0.79)

The Reid score of 4 would be a breakpoint to keep the sensitivity as high as possible without reducing the specificity. Table 3.6 shows the sensitivity, specificity, PPV and NPV for Reid score in predicting CIN 2 and above.

Table 3.6 Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value for Reid Score in predicting CIN≥2

Score	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value	Negative predictive value
Score 1 (n=506)	96.90% (92.30% - 99.10%)	15.00% (11.80% - 18.60%)	24.70% (21.00% - 28.70%)	94.40% (86.20% - 98.40%)
Score 2 (n=400)	94.60% (89.10% - 97.80%)	37.90% (33.40% - 42.60%)	30.50% (26.00% - 35.30%)	96.00% (92.00% - 98.40%)
Score 3 (n=310)	87.60% (80.60% - 92.70%)	56.00% (51.30% - 60.70%)	36.50% (31.10% - 42.10%)	94.00% (90.50% - 96.50%)
Score 4 (n=231)	72.90% (64.30% - 80.30%)	69.40% (64.90% - 73.70%)	40.70% (34.30% - 47.30%)	89.90% (86.20% - 92.90%)
Score 5 (n=159)	62.00% (53.10% - 70.40%)	82.40% (78.50% - 85.80%)	50.30% (42.30% - 58.30%)	88.30% (84.80% - 91.20%)
Score 6 (n=99)	45.70% (36.90% - 54.70%)	91.10% (88.00% - 93.50%)	59.60% (49.30% - 69.30%)	85.40% (81.90% - 88.40%)
Score 7(n=47)	22.50% (15.60% - 30.70%)	96.00% (93.70% - 97.60%)	61.70% (46.40% - 75.50%)	81.10% (77.50% - 84.40%)
Score 8 (n=18)	10.10% (5.50% - 16.60%)	98.90% (97.40% - 99.60%)	72.20% (46.50% - 90.30%)	79.20% (75.60% - 82.50%)

Below is the ROC curve illustrating the performance of each scoring system (Swede and Reid scores) [figure 3.5] comparing the two systems.

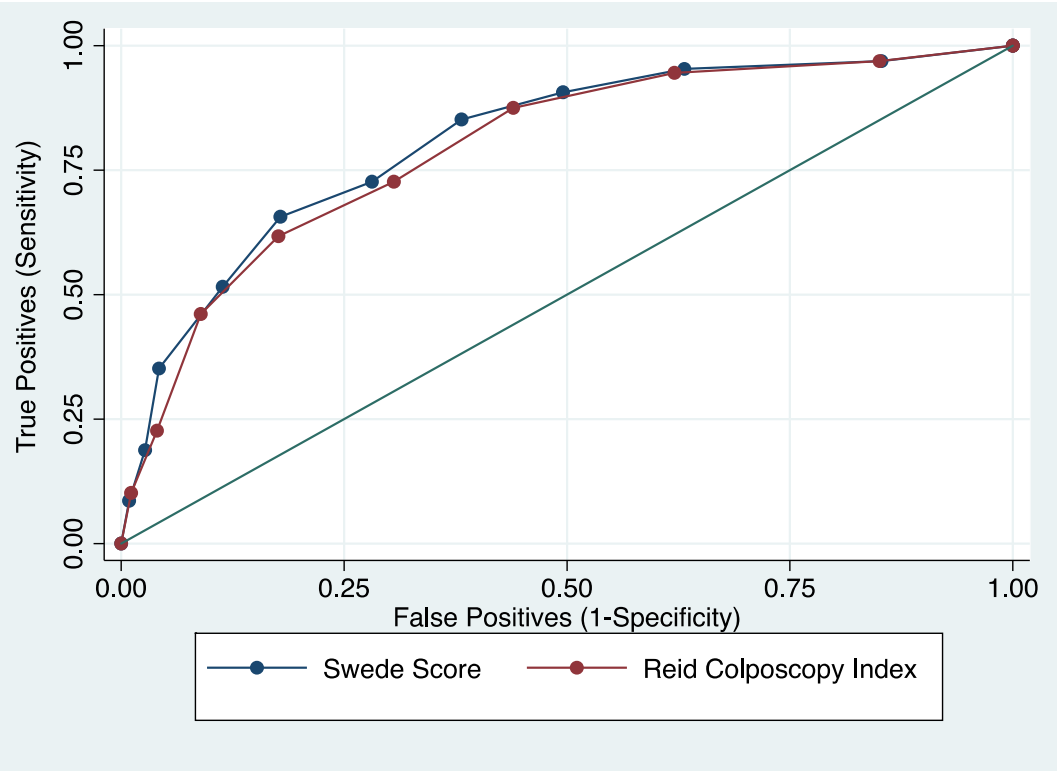

Figure 3.5 ROC graph of Sensitivity and Specificity of Total Reid and Swede Score

The area under the curve using the Swede is 0.81 and using the RCI is 0.79. In comparing the two systems, the Swede score is more accurate even though the Reid score does not fall into the category of a worthless test as illustrated in table 3.7 below. Even though they appear to be visually similar they have a statistically significant difference with a p value of 0.006 using the chi^2 test.

Table 3.7 Comparison of Total Swede and Total Reid Score

SCORING SYSTEM	Observations	Area	[95% Conf. Interval]
Total Swede score	576	0.81	0.76 - 0.85
Total Reid score	576	0.79	0.75 - 0.83

P = 0.006 (Chi^2)

The ROC curve below compares the various parameters within the Score and as can be seen in the graph below and the table that the "Iodine uptake" and the size of the lesion have the highest predictive values.

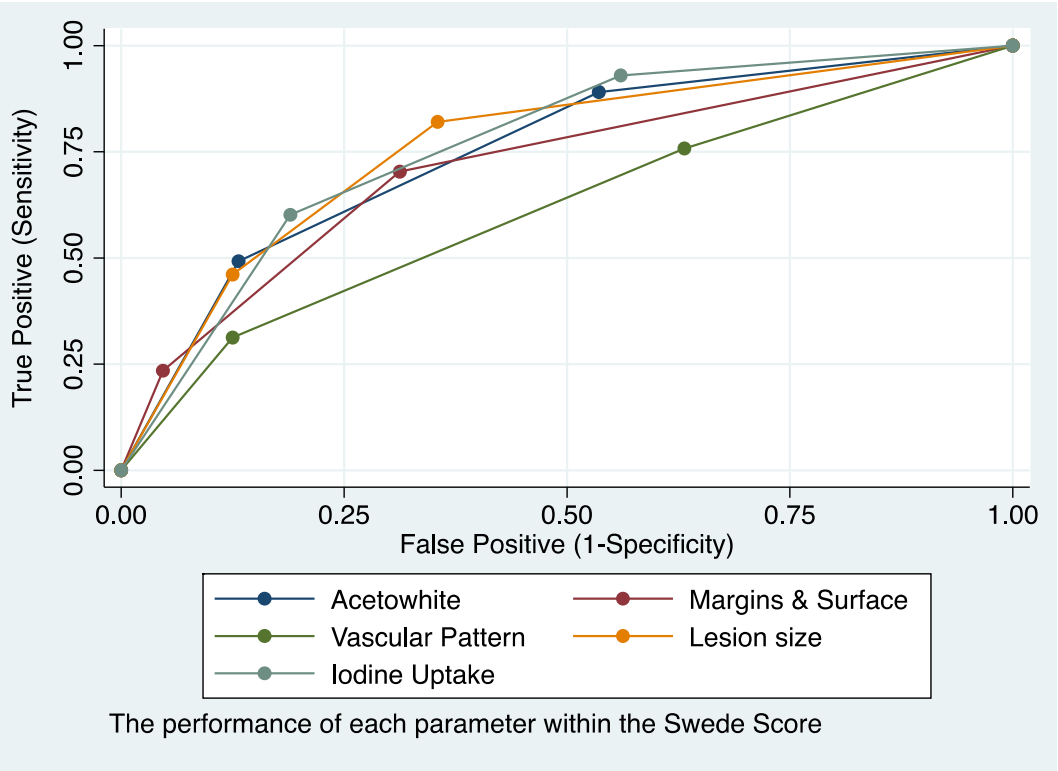

Figure 3.6 ROC graph comparing the parameters within the Swede Score.

Table 3.8 Swede score parameters

Swede score value (n=576)	Area	[95% Conf. Interval]
Acetowhite	0.75	0.71 - 0.79
Margins & surface of lesion	0.72	0.67 - 0.76
Vascular pattern	0.61	0.56 - 0.67
Lesion size	0.76	0.72 - 0.81
Iodine uptake	0.77	0.72 - 0.81

The ROC curves shown in figures 3.7 and 3.8 compares the Swede score and RCI with findings on cytology of Normal/ASCUS/LSIL versus those with HSIL/ASC-H/cannot exclude invasion. There was no statistical difference in accuracy of Swede scores or the RCI by the two categories of antecedent cytology.

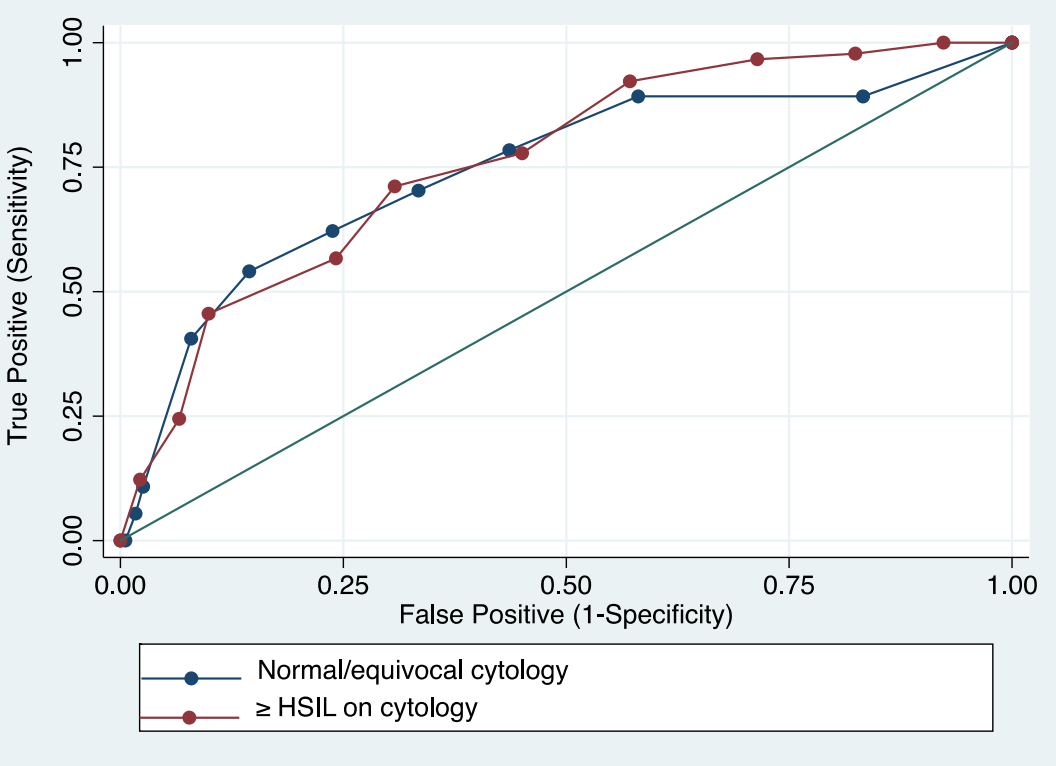

Figure 3.7 ROC graph comparing the Swede score and cytology.

Table 3.9 New CIN threshold for treatment of total Swede score by new cytology

Cytology	Observa-tions	Area	[95% Conf. Interval]
Normal/ASCUS/LSIL	390	0.74	0.65 - 0.83
HSIL/ASC-H/cannot exclude invasion	181	0.76	0.69 - 0.83

P = 0.76 (Chi^2)

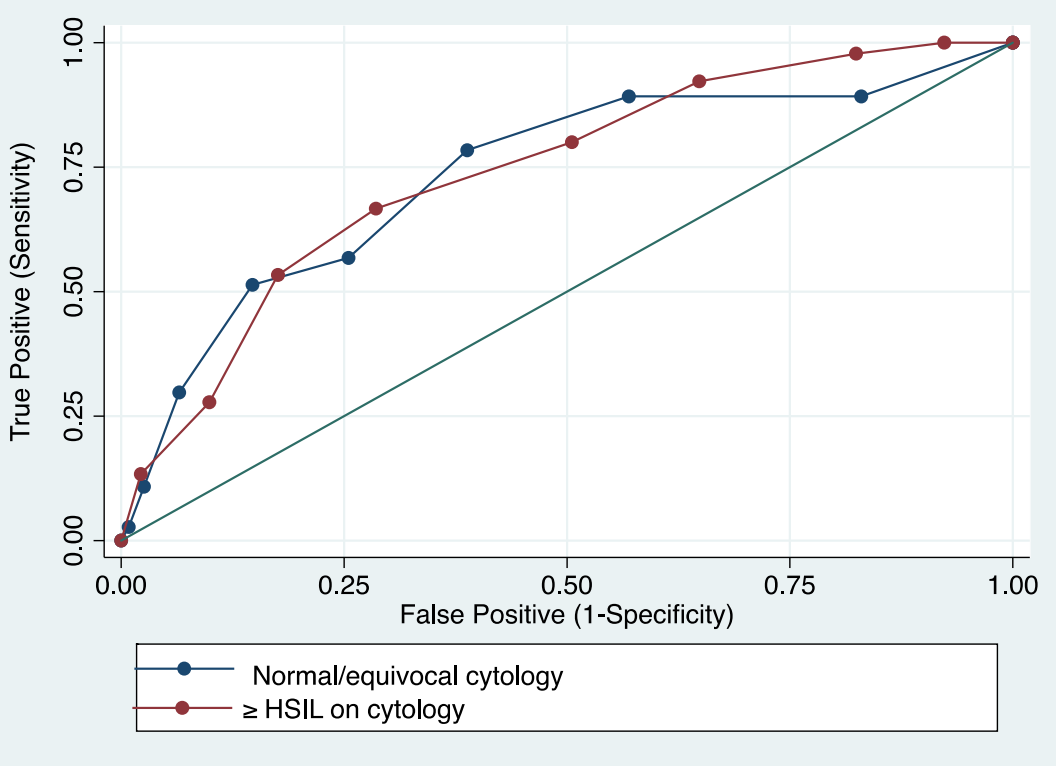

Figure 3.8 ROC graph comparing the Reid score and cytology findings.

Table 3.10 New CIN threshold for treatment of total Reid score by new cytology

Cytology	Observa-tions	Area	[95% Conf. Interval]
0	390	0.74	0.64 - 0.83
1	181	0.74	0.67 - 0.81

P = 0.94 (Chi^2)

CHAPTER 4

4.1. Discussion

Cervical cancer is a preventable condition, especially with the advent of effective screening, diagnostic and therapeutic procedures. Colposcopy is an essential tool in offering diagnostic and treatment modalities. Colposcopic indices like the Reid and Swede scores have been designed to overcome the subjectivity of colposcopy and are studied extensively. Newer international colposcopic terminology like the 2011 IFCPC nomenclature have been introduced and proposed as an alternative, however studies evaluating this method are very scanty.

In this study, the Swede score and the Reid Score for detecting CIN2+ in HIV infected women would lead to approximately 30% of women being over-treated and 30% under-treated in a 'see and treat' clinic. The difference in the area under the curve for the Swede and Reid scores was statistically significant, but clinically the scores would result in similar over- and under-call. The superiority of the Swede score may be in that it includes lesion size which had a similar AUC to iodine uptake in this study.

The size of the lesion has been found to be a good predictor of high grade disease in a prospective observational study by Munmany et al. which evaluated whether colposcopic measurement of the lesion size at diagnosis can predict the absence of dysplasia in a LLETZ specimen in women treated for SIL/CIN.[48] Kushwar et al. also showed a statistically significant correlation between the association of lesion size and CIN 2+ histology.[59] Another added advantage of the lesion size is that it can assist the Health worker to decide on the feasibility of treatment modality as described by Ranga et al.[66] The size of the lesion also assists with deciding which loop size to use clinically.

When comparing the different scores, studies have shown that they all perform well with no clear consensus on which one is superior. In the current study, the Swede score performed slightly better than the RCI with a statistically significant difference. This could be due to the addition of the lesion size on the Swede score. A retrospective analysis of 525 women by Li et al. in China comparing the RCI, Swede score and the IFCPC classification reported the

IFCPC to perform better than the other scores with sensitivity, specificity, PPV and NPV of 63.6%, 96.0%, 78.7% and 91.9% respectively for predicting HSIL on colposcopy.[69] Iodine uptake was found to be of significance in predicting CIN 2+ when using the Swede score in the current study, while iodine negativity was reclassified as a non-specific finding in the IFCPC classification.[69] Two studies in India found a high correlation between the Reid and Swede Scores, they used a cut-off score of 5 for the Reid score and 5 and 8 for the Swede score.[59,66] In the 'see and treat' setting where specificity is important in limiting over-treatment, both of these scores are sufficiently flexible to use a different threshold for immediate treatment. Using a Swede score of 8 would increase the specificity to 95.8% and a Reid score of 7 would increase the specificity to 96%.

Scoring systems like the Reid and Swede scores attempt to remove the subjectivity from Colposcopy.[56,61] The Swede score was evaluated in 261 pregnant women and had a specificity for HSIL of 52.9% using a score of 5.[64] A study in the UK of 200 women found a score of 5 or more to have a sensitivity of 75%, specificity of 73%, PPV of 65% and a NPV of 81%.[62] A more recent study done in India reported a sensitivity of 100% and specificity of 88.4% also using a Swede score of 5 and above.[66] A prospective study in Iran reported a sensitivity and specificity of 74% and 90.7% for CIN 2+, although their study was in a population where HIV was not mentioned or was not included.[57]

Most studies do not report the method of colposcopy used, often just stating that "acetowhiteness and vascular change" was assessed and making a colposcopic impression of disease. The sensitivity of colposcopic impression in a meta-analysis of 11 studies including 6370 women ranged from a sensitivity of 29-100% and a specificity of 12-88%.[44] A multicentre study showed that detection of high grade disease at baseline cytology with colposcopy had a sensitivity of 98% and 62.9% specificity.[53] Evidence shows that the sensitivity of colposcopy to distinguish normal from abnormal tissue is higher than the sensitivity in differentiating the difference between LSIL and HSIL. [45, 55] According to the ALTS study, this low sensitivity may be associated with more women being over-treated. There and there might also be high grade lesions that are missed at colposcopy.[45]

The performance of colposcopy in HIV positive women has been reported in three studies.[52,53,54] A study in Italy demonstrated that colposcopy was less accurate in HIV positive women than in HIV negative women. They suggested that inflammation of the cervix was responsible for this reduction in accuracy.[54] However Massad et al. demonstrated that when colposcopy was abnormal, the findings did not differ by patient's HIV status with a reported sensitivity, specificity, PPV and NPV of 29%, 96%, 26% and 96% respectively.[52] Kitchener et al. showed that colposcopy had a sensitivity, specificity and PPV of 98.0%, 62.9% and 21.6% respectively in accurately detecting high grade disease on women who were HIV seropositive.[53]

Another important finding in the current study is that there was no difference in the performance of the Swede or Reid score by antecedent Pap smear, that is having an equivocal Pap smear result versus HSIL or more severe. In a meta-analysis by Ebisch et al. when the antecedent Pap smear and colposcopic impression was high grade, the pooled overtreatment was 11.6% (95%CI: 7.8-15.3) and when the Pap smear and colposcopy was low grade the overtreatment was 46.4% (95%CI: 15.7-77.1%).[76]

The performance of both scores was also similar in women with or without HR-HPV.
The presence of HR-HPV in the cervix and vagina has been used for screening and has also been added to the armamentarium for screening in SA in the 2017 prevention of cervical cancer guidelines. [34,35] The presence of HPV 16 was previously shown to be associated with lesions that are more apparent at colposcopy.[11]

Primary prevention methods which include risk-modifying behaviour (prevention of smoking, good immunity, improved nutrition, improved sexual health practices and early initiation of ART in HIV positive women) and HPV prevention by vaccination can reduce the cervical cancer pre-cursor lesions.[35] The high incidence of any abnormal screening test either Pap smear, VIA, VILI or HPV testing in these women means that many HIV infected women will be referred to colposcopy, and that an accurate colposcopy will aid in the management of these women. Appropriate management of screen positive women is important not only to

ensure the appropriate use of resources, but also to reduce the potential adverse effects associated with treatment, such as preterm delivery and low birth weight.[38]

In the current study, histology was obtained by punch biopsy and not by excision of the transformation zone. It may be that a lesion may be missed with a punch biopsy.[72] However, this was ameliorated by the fact that four quadrant biopsies were taken and women in this study had a mean number of four biopsies, which has been shown to improve the low sensitivity.[73] This is in keeping with a number of studies demonstrating that the sensitivity of a colposcopic directed biopsy is much better and improved by taking two or more biopsies.[72,73] LLETZ has been found to be more accurate in diagnosing CIN when compared to colposcopically directed biopsy.[77,78]

4.2 Strengths

The strength of the study is that the colposcopy was performed by trained colposcopists. This is a procedure that should not only be performed by specialists, particularly in a country like SA where the burden of HIV and cervical cancer precursor is high. Another strength was the use of a rigorous approach by the HARP endpoint committee to ascertain the final histology result as histology is the gold standard of diagnosis.

4.3 Limitations

Any biases on the original study and its limitations will affect our study. We produced a Reid score from a Swede score based on data imputed using the 4 parameters within the Swede score. It may be that colposcopists trained in the Reid score could come to a different conclusion on scoring. Histology was obtained by punch biopsy and not by excision of the transformation zone. The study population excluded women over the age of 50. Age is a risk for cervical cancer and colposcopy is more difficult in menopausal women. The only way then to differentiate between the performances of the two scores would be to randomly allocate women to have the colposcopy performed using one or the other score.

4.4 Recommendations, implications for clinical practice and further research.

Scoring systems would assist in making colposcopy more accurate and comparable across different populations. Training in colposcopy should include the use of colposcopy scores.

We are of the opinion that the Swede score is superior because it would also assist in deciding the treatment modality that should be used. There is no additional cost to assessing lesion size. Considering that the colposcopic assessment is subjective and has a high likelihood of inter-observer variability, extensive training and experience is essential for Health Care Workers using this tool.[44,45]

The use of a score may assist in individualising treatment. In see and treat clinics a score with a high specificity may be better. These figures may also be used to counsel women on the risk of overtreatment and under-treatment.

However there are other factors which determine immediate treatment, such as a concern for loss to follow-up and inadequate colposcopy.

The number of HIV infected women with a positive screening test (VIA/VILI/HR-HPV or Pap smear) is so high that it may be that all HIV infected women should be referred to colposcopy. However colposcopy may be harmful as it may lead to anxiety and the taking of unnecessary biopsies. It may be important to evaluate colposcopy in HIV infected women by blinding the colposcopist to the screen result.

We would recommend using “see and treat” approach in women with a Swede score of 8 or more. For women in whom the Swede score is less than 8, their management should be based on whether they have completed their families and on the risks of defaulting.

4.5 Conclusion

This study shows that the Swede score when compared to the Reid score performs better in terms of accuracy for predicting CIN≥2 lesions. The addition of the lesion size has been shown to have an added advantage in the performance of the scoring. Both scores also demonstrated flexibility. There is a higher likelihood of HIV infected women to be referred for colposcopy as they have a higher incidence of cervical cancer precursor lesions. There was no difference in the performance of the Swede or Reid score by antecedent Pap smear and there was no difference in colposcopy findings on women with the presence of HR-HPV or no HR-HPV.

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APPENDICES

Appendix A: Data Sheet

Age:

Parity							
Employed	**Yes**		**No**				
Contraceptives	**COC**	**Injectables**		**Im-plant/IUD**	**Barrier**	**POP**	**None**
		Nore-thisterone	**DMPA**				

Viral load	**Lower than de-tectable limit**	**Value**	**Unknown**	
CD4 count	**Value**		**Unknown**	
ARVs	**Yes**		**No**	

ARVs period				
Smoking	**Yes**		**No**	

Referral Cytology	LSIL	HSIL	ASCUS	ASC-H	AGUS

Colposcopic Impression of Reid score	Acetowhitening	Vascular changes	Iodine staining	Margins

Swede score	Acetowhitening	Vascular changes	Iodine staining	Margins	Size of lesion

Transformation Zone	Type 1	Type 2	Type 3	Uncertain

Histology results	Normal	Inflammation	HPV	Malignancy (microinvasion)
	CIN 1	CIN 2	CIN 3	

Appendix B: Concept note

Details

Name of Applicant: Vusumuzi David Maringa

Name of Institution :(for students University name & address and degree *(where you are currently registered at)*:

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HARP collaborator (*if applicable*): Philippe Mayaud (LSHTM), Sinead Delany-Moretlwe (WRHI), Nicolas Meda (CRIS-UO) and Michel Segondy (UM1), plus any HARP co-investigators who are interested

Length of placement *(if applicable)*: n/a

Title of project: The Performance of The Reid Colposcopic Index and Swede score: Predicting CIN in women living with HIV-1 in South Africa .

Brief overview of project, including background & rationale.

Globally cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer deaths in females.[1] Cervical cancer is the second most common cancer in women after breast cancer in South Africa. In 2012, 266 000 women died of cervical cancer worldwide.[2] The incidence and mortality rates have decreased over the last 40 years in developed countries and this has been attributed to implementation of secondary prevention efforts such as effective screening, early diagnosis and treatment for dysplasia and early cancer.[3]

Cervical cancer develops as a result of persistent infection with a high-risk human papillomavirus infection (HR-HPV), commonly acquired through sexual transmission.[4] This causes dysplastic changes in the epithelia of the cervix, termed Cervical Intraepithelial Neoplasia (CIN). Most of these HR-HPV infections clear spontaneously and they never progress to CIN.[5] There

also seems to be a higher incidence of premalignant lesions in women living with HIV/AIDS (WLHA).[6] Adequate treatment of cervical dysplasia reduced the incidence of cervical cancer by 95%.[7] In South Africa "*see and treat*" clinics for the management of women with precursor lesions are common with treatment based on colposcopic diagnosis. Overtreatment in these settings is a concern. A referral criterion is different for HIV positive and negative women, with HIV positive women being referred with less severe lesions. This may mean that they will be at a greater risk of over treatment which can be associated with early pregnancy losses, prematurity and cervical stenosis in future.

Using a scoring system at colposcopy may make colposcopic diagnosis more accurate and thereby reduce overtreatment. Scoring systems will also allow comparison between different centers and different practitioners. Scores use vascular changes, surface and margin abnormalities. All scoring systems give a 0, 1 and 2 and these are combined to get a final score.

A method of diagnosing and classifying the cervical abnormalities at colposcopy utilizes the Reid Colposcopic Index (RCI), proposed by Reid and Scalzi.[8] However there is a later version called the "Modified Reid Index" endorsed by the International Agency for Research on Cancer (IARC) because the original Reid Index failed to detect CIN 2 or higher at levels expected. This method predicts the histological diagnosis on the basis of 4 colposcopic features (Colour of acetowhite area, Margin and surface of acetowhite lesion, Vessels and Iodine staining) and a score is given to predict the grade of CIN, it has a sensitivity of 72-92% and specificity of 86%.[9] The RCI has been shown to perform well and its use is necessary in low resource setting as an effective and simple clinical method of screening.[10]

Another scoring system called the Swede score (which includes the four parameters of a RCI plus the size of lesion).[11] The Swede score is a modification of the Reid scoring system and has been shown to have an advantage over the Reid because it redefined the remaining variables of Reid score and it is simple to use. In addition to the four Reid colposcopic features, the Swede score has an additional feature which is "size of the lesion". A Swede score of 8 or more has a sensitivity, specificity, positive and negative predictive values of 38%, 95%, 83% and 70% respectively for lesions which are CIN 2 or higher. A Chinese- Californian study, demonstrated that the grade of referral smear was a confounder for lesion size and

colposcopic impression of of high grade lesion became more accurate when lesion size is increased.[12]

However the RCI is the most commonly used colposcopic scoring system to predict the grade of the premalignant lesion and in a resource limited country with a high prevalence of disease burden, the modality of 'see and treat' can be used as it has been proven to be cost effective and can prevent patients from defaulting their follow up visits.[13,14]

Objectives of project, including methodology (no more than 300 words)

Primary objectives (HARP-specific):

This proposed sub-study of the HARP study is retrospective. The overall aim is:

To evaluate the RCI for the detection of CIN in HIV infected African women.

Specific Objectives:

1. To describe the prevalence of CIN2+ by RCI scores
2. To determine the performance (sensitivity, specificity, NPV and PPV) of the RCI score
3. To determine the association between the RCI score components with CIN2+
4. To compare with results from Swede score on the same women

Sample size:

We want to review the data of all the patients (SA- 624) who were enrolled in the HARP study

Methodology:

The HARP study enrolled 1238 (BF=615; SA=623) women living with HIV and AIDS (WLHA) between December 2011 to October 2012. Inclusion criteria were being HIV-1 seropositive, aged 25-50 years and resident in the city. Exclusion criteria were history of prior treatment

for cervical cancer, previous hysterectomy, and being pregnant or less than 8 weeks post-partum. The women were followed up 6-monthly up to 18 months. The main aim of the HARP study was to evaluate the diagnostic performance and cost effectiveness of cervical cancer screening methods to detect prevalent (at baseline) and incident/recurrent/persistent CIN-2+ (at 18-months) among WLHA.

Variables will be selected from the original data and used on a data sheet designed and compare how the RCI performed when associated with histological findings in diagnosing CIN 2+, and also determining how the size of the lesion (Swede score) influences the findings when compared to the RCI.

Research environment (and supervision for students), including a budget outline (if applicable) (no more than 300 words)

This sub-study is for my post-graduate Masters dissertation. I aim to begin data analysis at the beginning of November through to December, once Ethics committee has given permission to continue with study and the HARP study team has given permission to access data from the main study. This will be under the supervision of Prof Yasmin Adam (yasminadam@gmail.com) and Dr Langanani Mbodi (mlangi2005@yahoo.co.uk), who both work within the department of Obstetrics and Gynaecology at Chris Hani Baragwanath and Charlotte Maxeke Johannesburg Hospital respectively. Dr Admire Chikandiwa and Prof Sinead Delany-Moretlwe will also supervise this sub-study as they were investigators on the HARP study. Weekly meetings will be co-ordinated with them and they will guide me with the secondary analysis. Final write-up will be in January, with final submission for marking aimed for February 2017.

Intellectual property and authorship (no more than 300 words) (please state your intend on how the data will be used, i.e. thesis/dissertation, publications, conferences etc.)

The data will be primarily used for my masters dissertation.

An article from the thesis will be submitted to a South African or possibly an International scientific journal for publication. The results of the study will also help reinforcing policies in

our clinics and hospitals. Involvement of HARP investigators in this sub-study is welcomed. The HARP study team will be included in the authorship lists as well as any individual HARP investigator who is eligible for a co-authorship as specified in international authorship guidelines.

Note that: all data and tools used/developed will remain the intellectual property of the HARP Consortium. Subsequent consideration of publication of material generated with the research projects will be subject to agreement of the HARP Consortium. Guidelines of HARP and EC will apply. Approval by HARP's Project Steering Committee (PSC) will be sought before the start of the Project and at the time of dissemination of findings. HARP Consortium will have to be acknowledged as well as EC funding for the parent study.

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Appendix C: South African HARP study group Co-ordinators agreement

SOP: Access to data by external parties V2

Agreement

In terms of this agreement **Dr Dave Vusumuzi Maringa** will use the **HARP Study** data for the completion of analysis and writing of a **MMed thesis/research report** entitled *The Performance of The Reid Colposcopic Index and Swede scores in Predicting CIN in women living with HIV-1 (WLHA) in South Africa* which has been provisionally accepted by **Wits University**. The final version of the paper will be reviewed and accepted by **Prof Sinead Delany-Moretlwe** before final submission. The data will not be used for any other publications before consultation with Wits RHI.

We have read and accept these conditions.

Applicant 1

Name: Dr Dave Vusumuzi Maringa

Applicant Signature:

Date: 25/11/2016

Wits RHI Representative

Name: Dr Admire Chikandiwa

Applicant Signature: 25/11/2016

Date:

Appendix D: Ethics Approval

R14/48 Dr Vusimuzi David Maringa et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161046

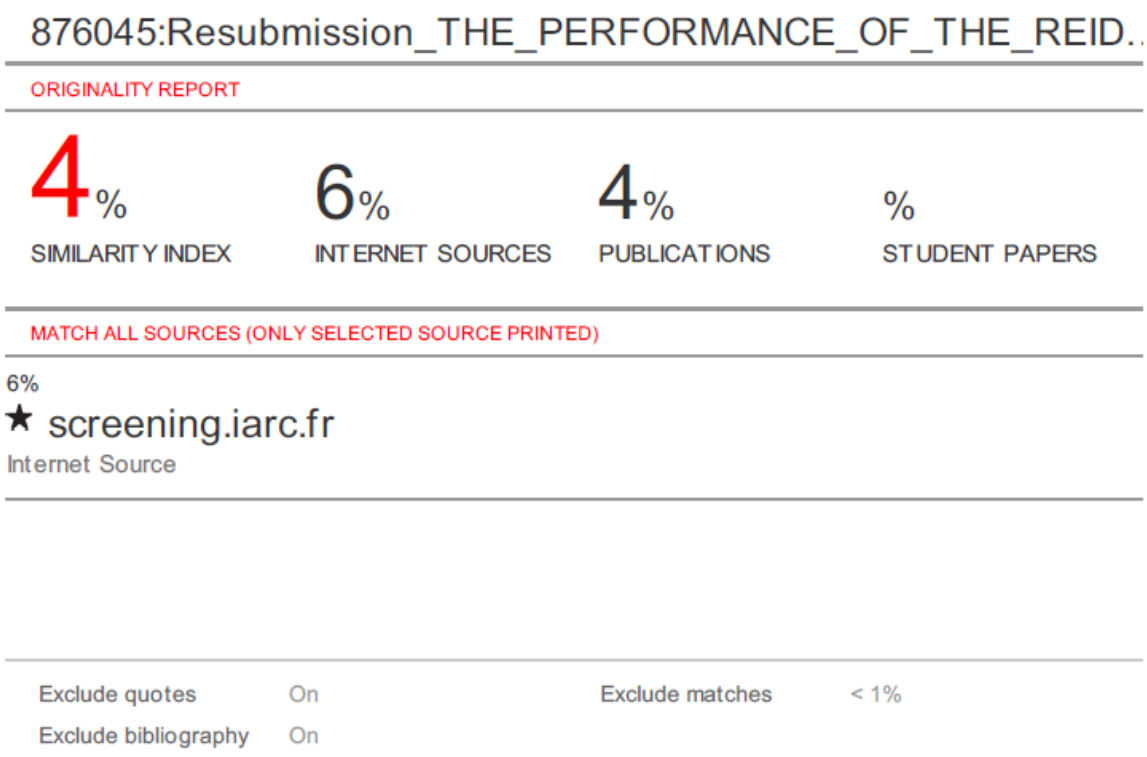
NAME: (Principal Investigator)	Dr Vusimuzi David Maringa et al
DEPARTMENT:	Obstetrics and Gynaecology Primary Health Clinics, Hillbrow, Johannesburg, South Africa
PROJECT TITLE:	Perfomance of Reid Colposcopy Index and Swede Score: Predicting CIN in Women Living with HIV-1 in South Africa
DATE CONSIDERED:	28/10/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Langanani Mbodi and Prof Yasmin Adam
APPROVED BY:	Prof A Dhai, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/12/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Philip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Appendix E: Turnitin Report



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