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Natural history of cervical intraepithelial neoplasia-2 in HIV-positive women of reproductive age

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Abstract

Objective: To evaluate the natural history of treated and untreated cervical intraepithelial neoplasia-2 (CIN2) among HIV-positive women.

Methods: Participants were women enrolled in the Women's Interagency HIV Study between 1994 and 2013. 104 HIV-positive women diagnosed with CIN2 before age 46 were selected, contributing 2,076 visits over a median of 10 years (IQR 5–16). The outcome of interest was biopsy-confirmed CIN2 progression, defined as CIN3 or invasive cervical cancer. CIN2 treatment was abstracted from medical records.

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DECLARATION OF INTERESTS

J.M.P. owns stock options in Ubiome; receives grant support and acts as consultant for Antiva; receives grant support, acts as consultant and owns stock in Agenovir; receives grant support, travel support and is on an advisory board for Merck & Co.

Conflicts of Interest Statement: J.M.P. owns stock options in Ubiome; receives grant support and acts as consultant for Antiva; receives grant support, acts as consultant and owns stock in Agenovir; receives grant support, travel support and is on an advisory board for Merck & Co.

All other authors report no conflicts of interest.

IRB Status: Approved under at all sites before study began.

Results: The majority of women were African American (53%), current smokers (53%) and had a median age of 33 years at CIN2 diagnosis. Among the 104 HIV-positive women, 62 (59.6%) did not receive CIN2 treatment. Twelve HIV-positive women (11.5%) showed CIN2 progression to CIN3; none were diagnosed with cervical cancer. There was no difference in the median time to progression between CIN2-treated and -untreated HIV-positive women (2.9 vs. 2.7 years, p=0.41). CIN2 treatment was not associated with CIN2 progression in multivariate analysis (aHR [adjusted hazard ratio] 1.82; 95% CI [confidence interval] 0.54, 7.11), adjusting for combination antiretroviral therapy (cART) and CD4+ T cell count. In HIV-positive women, each increase of 100 CD4+ T cells was associated with a 33% decrease in CIN2 progression (aHR 0.67; 95% CI 0.47, 0.88), adjusting for CIN2 treatment and cART.

Conclusions: CIN2 progression is uncommon in this population, regardless of CIN2 treatment. Additional studies are needed to identify factors to differentiate women at highest risk of CIN2 progression.

Precis:

Cervical intraepithelial neoplasia-2 progression is uncommon in HIV-positive women of reproductive age on combination antiretroviral therapy over 10 years, regardless of cervical intraepithelial neoplasia-2 treatment.

Keywords

cervical intraepithelial neoplasia; cervix; disease progression; HIV; antiretroviral therapy; CD4 lymphocyte count; prospective studies; cohort studies

INTRODUCTION

Women living with HIV have a higher risk of cervical intraepithelial neoplasia (CIN) and cervical cancer, as well as higher risk of infection by human papillomavirus (HPV), compared to HIV-negative women [1–5]. Currently, most women diagnosed with CIN2 or more advanced cervical disease are counseled to undergo excision of the abnormal tissue, regardless of HIV status [6,7]. However, there is evidence that treatment by excision can affect cervical competence resulting in subsequent pregnancy complications [8], including preterm delivery [9,10]. Women living with HIV would then be disproportionally affected by these adverse treatment effects given the higher risk of CIN development. Advances in HIV therapies have improved the overall health of HIV-positive individuals and effectively prevented mother-to-child transmission in the US [11], with approximately 8,500 American women with HIV giving birth annually [11]. Thus, studying the risk of CIN2 progression among HIV-positive women of reproductive age can provide more precise guidance on treatment options for women and their health-care providers.

In this study, we evaluated the natural history of CIN2 among a group of women of reproductive age enrolled in the Women's Interagency HIV Study (WIHS), a longstanding observational cohort of HIV-positive and high-risk HIV-negative women. To provide additional guidance for HIV-positive women of reproductive age with CIN2, we sought to

ascertain the risk of CIN2 progression, determine the time it takes for CIN2 progression to occur, and identify factors associated with CIN2 progression.

METHODS

Data for this study were obtained from the Women's Interagency HIV Study (WIHS), a prospective observational cohort study in which HIV-positive and high-risk HIV-negative women were enrolled at six sites (Bronx and Brooklyn, NY; Chicago, IL; Los Angeles and San Francisco, CA; and Washington, DC) during three recruitment phases: 1994–1995, 2000–2001, and 2012–2013 [12,13]. Data for the current study spanned from October 1, 1994 to September 30, 2013 (total enrollment: 2,599 HIV-positive and 912 HIV-negative women). The study design of the WIHS is detailed elsewhere [12,13]. Briefly, women visit a study site every six months. During each visit, physical and obstetric/gynecologic examinations are performed and biological specimens are collected. A Pap test was obtained at each visit from visit 1 (starting October 1, 1994) to visit 37 (ending March 31, 2013). Beginning with visit 38 (occurring April 1, 2013 to September 30, 2013), women at low risk of CIN (defined as 3 consecutive normal Pap tests) have Pap testing done annually. Colposcopy and biopsy are performed for all women who have an abnormal Pap test (atypical squamous cells of undetermined significance (ASC-US+) or more severe) or have abnormal findings on gynecologic exam. Information on CIN treatment is collected through medical record abstraction. Treatment is not offered through the WIHS, as the study is solely observational, however study staff refer participants to seek treatment and care from their providers. Written informed consent was obtained from all WIHS participants. The local institutional review boards reviewed and approved all study-related activities at each WIHS site.

A total of 251 women with biopsy-confirmed cervical CIN2 before the age of 46 (the cutoff used to include women of reproductive age) were included. These 251 women must have had an adequate colposcopy at the time of CIN2 biopsy, where the pathologist noted the lesion was visible, to ensure an accurate biopsy. Of the 251 initially identified women, 106 were excluded due to a biopsy-confirmed diagnosis of CIN3, adenocarcinoma in situ, or invasive cervical cancer in a visit prior to the CIN2 diagnosis. A further 27 women were excluded who did not have at least two follow-up evaluations for cervical disease by Pap test or histology within two years post-CIN2 diagnosis. Thus, 118 women (104 HIV-positive and 14 HIV-negative) were included in the present study (Figure 1).

Three potential outcomes were defined: progression, regression, or stable disease. CIN2 disease regression was defined as either: i) a lower grade lesion than CIN2 on all subsequent biopsies (CIN1 or no abnormality detected) or ii) normal Pap tests across all follow up visits after the index visit. Disease progression was defined as any cervical disease greater than CIN2 by histology at least six months after the index visit—CIN3 or cervical cancer diagnosis within six months was considered CIN2 misclassification at the initial visit and not included in further analyses. Stable disease was defined as having CIN2 persist in any follow-up visits after the index visit.

Covariates included demographic variables, behavioral factors, reproductive and gynecologic medical history, and HIV-related health information. Demographic variables included race (white [reference], Black, Hispanic, other) and age (continuous). Behavioral factors included smoking status (never smoker [reference], current smoker, former smoker). Categorical number of current sexual partners were considered by gender and number (Table 1), but condensed into total partner number within the previous 6 months for regression analyses. Reproductive and gynecologic medical characteristics included treatment of CIN2 received on a date within the same 6-month WIHS visit window (yes/no), percentage of abnormal cells at colposcopy (less than 25% [reference], 25-less than 50%, 50-less than 75%, greater than 75%), and overall impression of cervix at colposcopy (normal [reference], abnormal, but no squamous intraepithelial lesions (SIL), low grade, high grade neoplasia). Current pregnancy, cervical exam adequacy (satisfactory, endocervical speculum used to visualize squamocolumnar junction, or unsatisfactory), and Pap test results (normal, ASC-US, atypical squamous cells cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL)) were considered as covariates. HIV-related variables of interest included combination anti-retroviral (cART) use in visit (yes/no), CD4 T cell count in visit or plasma HIV viral load in visit.

Use of cART [14], CD4+ T cell count [14], plasma HIV RNA level, number of sexual partners [14,15], and smoking status [14,15] were considered time-varying covariates. CIN2 treatment was analyzed as a time-varying variable coded as follows: 1) for those treated within six months of the index visit, the index visit and all follow-up visits were “CIN2 treated”; 2) for those who began treatment in any follow-up visit, the visits before treatment were “untreated” and the visit on or after treatment initiation was “treated”; and 3) for those never treated, all visits were “untreated”.

Chi-square Test or Fisher’s Exact test were used to compare categorical variables and Student t test or Wilcoxon Rank-Sum Test were used to compare numeric variables. The Kaplan-Meier method was used to describe cumulative hazard of CIN2 progression following the index visit, stratified by CIN2 treatment. Inverse probability-weighted estimation was used to estimate the effectiveness of CIN2 treatment [16], including the following covariates: age, race, smoking status, cART use, pregnancy, partner number, CD4+ T cell count, and HIV plasma viral load (data not shown). Inverse probability weighting did not demonstrate differences between the CIN2 treated and untreated groups, thus Cox proportional hazards models, where covariates of interest can be explored rather than merely controlled for, were used. Cox proportional hazards models with time dependent covariates were used to estimate associations of risk factors with time to CIN2 progression. Variables significant in the univariate analysis ($p<0.05$) were included in the multivariate analysis. Participants were followed to either CIN2 progression or censored events (e.g. death, loss to follow up, reaching the most recent visit). An alpha level of 0.05 and two-tailed tests were used to determine significance in all statistical tests. All statistical analyses were carried out using SAS 9.3 (SAS Inc., Carey, NC).

A sensitivity analysis was conducted to determine whether diagnoses of “non-specific dysplasia” by biopsy could be categorized as progression events. We re-analyzed data with

"non-specific dysplasia" as a progression event, using the Kaplan-Meier and Cox proportional hazard models. We found cART use was significantly associated with, and protective against, the hazard of CIN2 progression in multivariate analysis (aOR 0.20; 95% CI 0.05, 0.71), controlling for CIN2 treatment and CD4+ T cell count, however all other findings were similar to the main analysis. We thus present the more stringent analysis that excludes "non-specific dysplasia" diagnoses as progression events.

RESULTS

Among the 2,559 HIV-positive and 912 HIV-negative women in the WIHS at the time of this analysis, 104 (4.1%) HIV-positive and 14 (1.5%) HIV-negative women met our inclusion criteria (Figure 1). The 118 women contributed 2,379 visits in total (2,076 HIV-positive and 303 HIV-negative). Among these women, 53% were Black, 34% were Hispanic, and 53% were current smokers at the time of the index visit (Table 1). Women living with HIV were significantly older than HIV-negative women (33 vs 28 years, $p < 0.001$); all other examined socio-demographic characteristics and smoking status were similar between HIV-positive and HIV-negative women (Table 1).

The likelihood of ever-receiving CIN2 treatment during the follow-up period differed by HIV status, but did not reach statistical significance (57.1% HIV-negative vs 40.4% HIV-positive, $p = 0.26$). Among women living with HIV, index-visit Pap test results differed significantly between those treated vs. untreated for CIN2 ($p = 0.02$) (Table 2). Seven women with a normal Pap test were examined by colposcopy. Although it is not routine practice to perform a colposcopy following a normal Pap test, 5 of these 7 women had an indication for colposcopy through an LSIL or ASC-US finding within the previous 6 months at WIHS. One additional woman was referred to colposcopy as it was routine for first visit in the core WIHS, and for one woman the colposcopy was for visible cervical lesions. The majority of CIN2-treated HIV-positive women had low-grade squamous intraepithelial lesions (LSIL) on Pap test at the index visit (Table 2). However, colposcopy findings, age, CD4+ T cell count, plasma HIV RNA level, and cART use at the index visit were similar between CIN2 untreated and treated HIV-positive women (Table 2). CIN2-treated and -untreated HIV-positive women were also followed for similar time periods after the initial diagnosis (median 10.0 years vs. 10.1 years).

Overall, 12.7% of women in the study progressed within the median 10-year follow-up. CIN2 progression was seen in 11.5% of HIV-positive women and 21.4% of HIV-negative women (Table 1). None of the women in the study progressed to cervical cancer during follow up. Cervical biopsy results at each 6-month visit are shown in Appendix 1 for the 12 HIV-positive women who demonstrated cervical disease progression, 8 (66.6%) of whom received CIN2 treatment before progression.

Kaplan-Meier analysis was used to explore the time to CIN2 progression in HIV-positive women treated vs. untreated for CIN2. There was no significant difference in the number of years to CIN2 progression (3.9 vs. 3.0, $p = 0.34$) (Table 2), but the cumulative hazard of CIN2 progression was significantly different between women treated vs. untreated for CIN2 (23.5% vs. 7.2% $p = 0.04$) (Figure 2). Cumulative hazards of CIN2 progression in those

CIN2-treated vs. –untreated at 2 years was 10.0% vs. 3.4%, by 5 years was 13.2 vs. 7.2%, and at 8 years was 23.5% vs 7.2%. However, the Kaplan-Meier analysis does not adjust for other cofactors of interest.

There was no effect of CIN2 treatment on cervical disease progression on multivariate analysis (Table 3). Similarly, inverse probability weighting confirmed the lack of treatment effect on CIN2 progression in HIV-positive women (HR 0.95, $p = 0.88$).

Cox proportional hazards models were used to investigate factors associated with CIN2 progression (Table 3). An increase of 100 CD4+ T cells was associated with a 33% decrease in CIN2 progression (aHR 0.67; 95% CI 0.47, 0.88), but CIN2 treatment and cART use were not significantly associated with CIN2 progression in these models adjusted for CD4 count (Table 3).

Overall, CIN2 regression was the most common result during follow-up, occurring among 73/118 (61.9%) women, with 60.6% of HIV-positive and 71.4% of HIV-negative women exhibiting cervical disease regression (Table 1). Thirty HIV-positive and HIV-negative women demonstrated stable CIN2 diagnosis, where CIN2 persisted in a follow-up visit.

DISCUSSION

Within the long-term, multi-site observational WIHS cohort, we found low rates of CIN2 progression over a median 10 year follow-up period in both HIV-positive and HIV-negative women, regardless of whether CIN2 treatment was recieved. The strongest predictor of CIN2 progression among HIV-positive women in our study related to HIV immunologic status, with higher CD4+ T cell counts over time showing a protective effect against CIN2 progression. Additionally, a sensitivity analysis that included “non-specific dysplasia in biopsy” diagnoses as progression events found that the hazard of CIN2 progression decreased with sustained cART use. cART use and well-maintained CD4+ T cell counts have previously been associated with regression of cervical abnormalities among women living with HIV [14,16–18]. Although cigarette smoking has been shown to associate with the development of cervical cancer [20], this variable was not included in our multivariate model as it did not meet the pre-specified significance level in univariate analysis. We may not have identified this important modifiable variable as a risk factor for CIN2 progression in our study due to a small sample size.

We identified high rates of CIN2 regression, similar to what is reported in the literature among the general population [20,21]. Regression of CIN2+ in women living with HIV has been previously reported at 24% over 12 months and 46% over a median of 17 months [16]. In our study, 60.6% of HIV-positive women with CIN2 showed disease regression over a median 10 years follow-up, with an additional 27.9% demonstrating stable disease. However, it should be noted that per the LAST guidelines, the recommended nomenclature now uses a two tier system (CIN1 (low grade squamous intra-epithelial lesion (LGSIL)) and CIN2+3 (high grade squamous intraepithelial lesion (HGSIL)) that was not in place during the majority of data collection for the current study [22].

Due to the small numbers of HIV-negative women diagnosed at CIN2 in this study, we were unable to compare disease progression and regression rates by HIV status. We note that women living with HIV had lower rates of CIN2 treatment compared to HIV-negative women, although this was a non-significant 17% difference between groups. Given the small proportion of HIV-negative women in the current study, further research is needed to ensure that engagement, retention, and access to care related to HIV status are not contributing to discrepancies in cervical disease treatment in larger populations.

Our study benefits from a strict definition of CIN2, in an attempt to minimize disease misclassification given the noted inter-observer variability in the pathology assessment of CIN2 or CIN3 [6]. The sensitivity analysis with a broader definition of cervical disease progression (inclusion of “non-specific dysplasia” in cervical biopsy as a progression event) had results that were similar to the current analysis, except that cART use became significantly associated with a reduced risk of CIN2 progression. This reinforces the conclusion that progression is a less common event for women receiving antiretroviral therapy with well-controlled HIV.

The current study also benefits from a long follow-up period; women were followed for a median of 10 years after the initial CIN2 diagnosis. This extended period of follow-up is critical in characterizing the natural history of cervical neoplasia, given the relative slow progression typically associated with this disease. However, the current analysis is limited by the lack of concurrent HPV typing, which is now typically used to guide CIN2/CIN3 treatment decisions. Additionally, staining for p16INK4a, a biomarker associated with high-risk HPV oncogenic activity [21] was not feasible as cervical biopsies were not banked. Future research should focus on biomarkers to distinguish women at high risk of progression versus regression among women classified as HGSIL under the LAST guidelines [22].

A large proportion of women reported no CIN2 treatment in the current study despite the recommendations for treatment as standard-of-care. The WIHS does not document reasons for lack of treatment, whether they were provider selection bias, insurance and/or financial barriers, a woman’s personal choice to defer treatment, or under-reporting of CIN2 treatment by study participants. Further, data capture on treatment may have been incomplete, as treatment is not offered through WIHS. Thus details are obtained through medical record abstraction only. CIN2 treatment was not randomized in this study, thus confounding by indication may play a role in the finding of non-association between CIN2 treatment and disease progression. Pap test results may have influenced CIN2 treatment decisions for women in the analysis, as Pap results differed significantly between those treated or untreated.

CONCLUSION

In summary, the decision to use surgical treatment for management of cervical tissue abnormalities in HIV-positive women of reproductive age needs to be balanced against considerations of future childbearing, as CIN treatment may be associated with adverse reproductive outcomes [8–10]. Our findings of substantial regression and limited progression of CIN2 among HIV-positive women of reproductive age with viral suppression

challenges the current paradigm of immediate cervical resection, however further research is warranted to identify the subset of women at risk for progression. Future research should incorporate concurrent HPV testing with or without measurement of biomarkers such as E6/E7 messenger RNA, p16 staining, or related immune factors to differentiate women at highest risk of progression versus those who are unlikely to progress with conservative management in the era of effective antiretroviral therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

aHR	Adjusted hazard ratio
ASC-H	Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
cART	Combination antiretroviral therapy
CD4 T cells	Cluster of differentiation-4 T cells
CIN	Cervical intraepithelial neoplasia, graded CIN1, CIN2, CIN3
CI	Confidence interval
HIV	Human immunodeficiency virus

HPV	Human papillomavirus
HR	Hazard ratio
HSIL	High-grade squamous intraepithelial lesion
IQR	Interquartile range
LSIL	Low-grade squamous intraepithelial lesion
NIH	National Institutes of Health
RNA	Ribonucleic acid
SIL	Squamous intraepithelial lesion
US	United States
WIHS	Women's Interagency HIV Study

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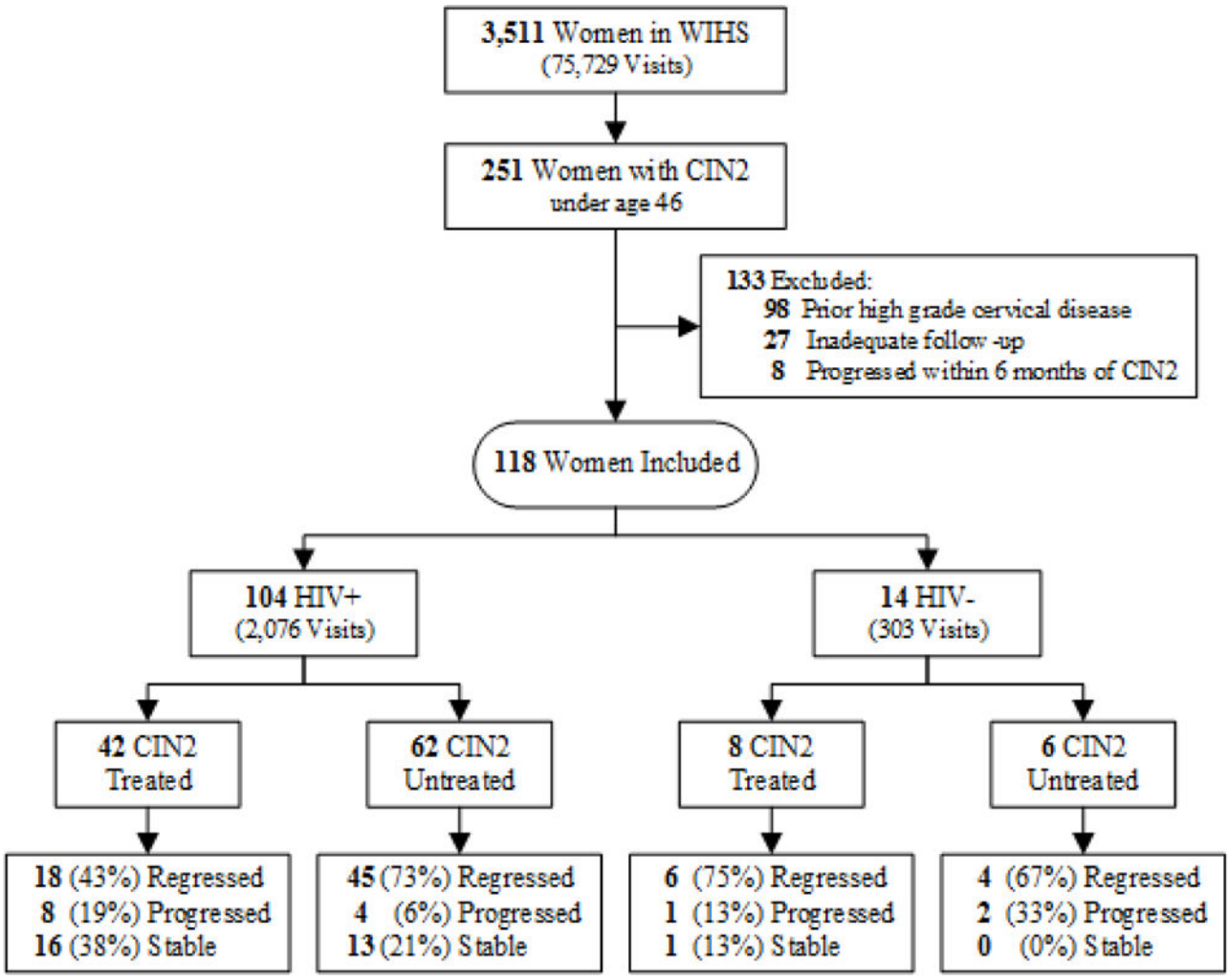
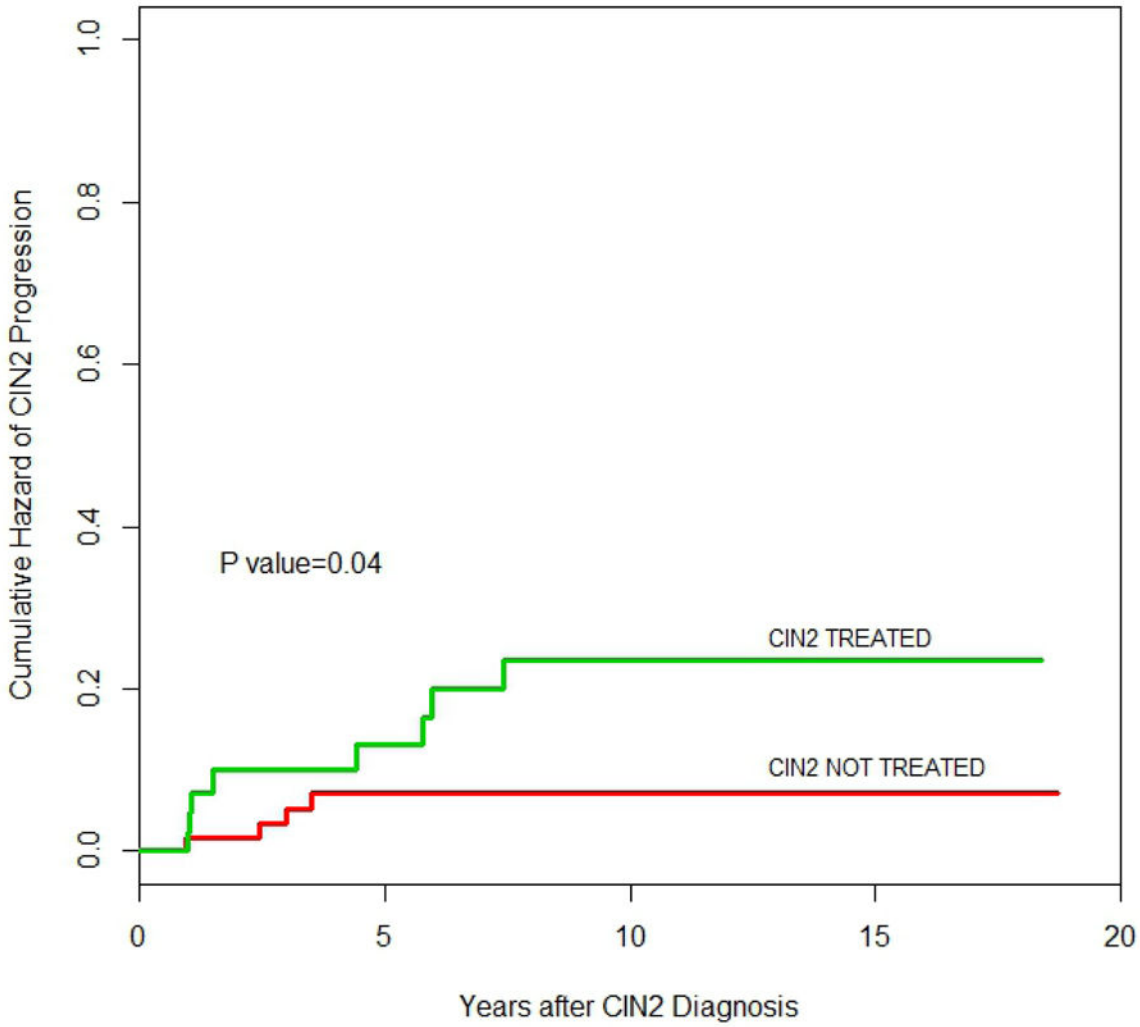


Figure 1:

Flowchart of study population determination from the WIHS. Cervical intraepithelial 431 neoplasia-2 (CIN2) regression defined as a lower grade lesion than CIN2 on all subsequent 432 biopsies or negative Pap tests across all follow-up visits; CIN2 progression defined as any 433 cervical disease greater than CIN2 by histology at least six months after the index visit. Stable 434 disease was defined as having CIN2 persist in any follow up visits after the index visit. WIHS = 435 Women's Interagency HIV Study.



No. at risk	Year 0	Year 5	Year 10	Year 15
CIN2 Treated	42	27	16	10
CIN2 Untreated	62	46	31	16

Figure 2:

Cumulative hazard of CIN2 progression for HIV-positive women, stratified by CIN2 438 treatment. CIN2 progression defined as any cervical disease greater than CIN2 by histology at 439 least six months after the index visit. CIN2 = Cervical intraepithelial neoplasia-2.

Table 1:

Characteristics of WIHS Women of Reproductive Age with a CIN2 Diagnosis, Stratified by HIV Status.

Variable, No. (%)	Total (n=118)	HIV+ (n=104)	HIV- (n=14)	*p*-value[a]
Follow-up status				0.18
Progression	15 (12.7)	12 (11.5)	3 (21.4)	
Regression	73 (61.9)	63 (60.6)	10 (71.4)	
Stable	30 (25.4)	29 (27.9)	1 (7.1)	
CIN2 Treated, ever	50 (42.4)	42 (40.4)	8 (57.1)	0.26
Race				0.67
White	9 (7.6)	9 (8.7)	0 (0)	
Black	63 (53.4)	54 (51.9)	9 (64.3)	
Hispanic	40 (33.9)	36 (34.6)	4 (28.6)	
Others [b]	6 (5.1)	5 (4.8)	1 (7.1)	
Smoking status [c]				0.58
Never smoker	38 (32.2)	32 (30.8)	6 (42.9)	
Current smoker	63 (53.4)	57 (54.8)	6 (42.9)	
Former smoker	17 (14.4)	15 (14.4)	2 (14.3)	
Currently pregnant [c]	2 (1.7)	2 (1.9)	0 (0)	1.0
Current male partner(s) [c]				0.42
0	17 (14.4)	15 (14.4)	2 (14.3)	
1	84 (71.2)	74 (71.2)	10 (71.4)	
2	15 (12.7)	14 (13.5)	1 (7.1)	
3	2 (1.7)	1 (0.9)	1 (7.1)	
Current female partner(s) [c]				1.0
0	115 (97.5)	101 (97.1)	14 (100)	
1	3 (2.5)	3 (2.9)	0 (0)	
Age, median (IQR) [c]	32.3 (26.8, 38.2)	33.5 (28.1, 38.4)	26.3 (23.3, 31.1)	<0.001

Abbreviation: WIHS, Women's Interagency HIV Study; CIN2, cervical intraepithelial neoplasia; HIV, human immunodeficiency virus; SD, standard deviation

[a]Chi-Square or Fisher's Exact test was used for categorical data; Wilcoxon Rank-Sum Test was used for numerical data.

[b]Includes Asian/Pacific Islander, Native American/Alaskan Native and Other

[c]These variable reported for the index visit--the first visit in which CIN2 was diagnosed.

Table 2:

Medical Characteristics of the WIHS HIV-Positive Women at CIN2 Initial Diagnosis, by CIN2 Treatment Status.

Variable, No. (%)	Total (n=104)	CIN2 Treated (n=42)	CIN2 Untreated (n=62)	*p*-value[a]
Follow-up status				
Progression	12 (11.5)	8 (19.1)	4 (6.5)	0.01
Regression	63 (60.6)	18 (42.9)	45 (72.6)	
Stable	29 (27.9)	16 (38.1)	13 (20.9)	
Cervical exam adequacy:				
Satisfactory	91 (87.5)	34 (80.9)	57 (91.9)	0.10
ES	13 (12.5)	8 (19.1)	5 (8.1)	
% Abnormal cells at colposcopy:				
0	0 (0)	0 (0)	0 (0)	
<25	47 (45.2)	20 (47.6)	27 (43.6)	
25 - <50	32 (30.8)	14 (33.3)	18 (29.0)	0.57
50 - <75	8 (7.7)	4 (9.5)	4 (6.5)	
>75	3 (2.9)	0 (0)	3 (4.8)	
Missing	14 (13.5)	4 (9.5)	10 (16.1)	
Impression of cervix:				
Normal	3 (2.9)	1 (2.4)	2 (3.2)	
Abnormal, but no SIL	15 (14.4)	4 (9.5)	11 (17.4)	
Low grade	73 (70.2)	31 (73.8)	42 (67.7)	0.71
High grade	13 (12.5)	6 (14.3)	7 (11.3)	
Invasive	0 (0)	0 (0)	0 (0)	
CIN2 treatment at index visit	28 (26.9)	28 (66.7)	0 (0)	*b*
cART use in index visit	27 (25.9)	11 (26.2)	16 (25.8)	0.97
Pap test results in index visit:				
Normal	7 (6.7)	0 (0)	7 (11.3)	
ASC-US	34 (32.7)	11 (26.2)	23 (37.1)	
ASC-H	0 (0)	0 (0)	0 (0)	0.02
LSIL	58 (55.8)	29 (69.1)	29 (46.8)	
HSIL	3 (2.9)	2 (4.8)	1 (1.6)	
Missing	2 (1.9)	0 (0)	2 (3.2)	
Total Follow-up years, median (IQR)	10.1 (5.2, 16.1)	10.0 (3.3, 16.6)	10.1 (5.7, 15.2)	0.83
Years to progression, median (IQR)	2.7 (1.0, 5.1)	2.9 (1.0, 5.8)	2.7 (1.7, 3.2)	0.41
Age in index visit, mean (SD)	33.1 ± 6.4	33.8 ± 5.9	32.7 ± 6.7	0.41
CD4 T cells in index visit, mean (SD)	348.8 ± 232.6	332 ± 238.7	359.7 ± 230	0.56
Log_{10} Viral load in index visit, mean (SD)	3.9 ± 1.3	4.0 ± 1.2	3.8 ± 1.4	0.45

Abbreviations: WIHS, Women's Interagency HIV Study; HIV, human immunodeficiency virus; CIN2, cervical intraepithelial neoplasia-2; ES, endocervival speculum used to visualize squamocolumnar junction; SIL, squamous intraepithelial lesion; ASC-US, atypical squamous cells of

undetermined significance; ASC-H, Atypical squamous cells, cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade intraepithelial lesion; IQR, interquartile range; SD, standard deviation

[a] Chi-Square or Fisher's Exact test was used for categorical data; two-Sample t-test or Wilcoxon Rank-Sum Test was used for numerical data.

[b] *p*-value cannot be determined as all same-visit treatment events occurred within the CIN2 treated category

Table 3:

Hazard Ratios of CIN2 Progression in HIV-Positive Women of Reproductive Age in the WIHS (n=104).

Variable	Univariate HR (CI)	Multivariate HR (CI)[c]
CIN2 treatment ever	3.28 (1.03 – 12.30)	1.82 (0.54 – 7.11)
Age at CIN2 diagnosis	1.01 (0.99 – 1.20)	
Race		
White	Reference	
Black	0.70 (0.18 – 4.65)	
Hispanic	0.87 (0.13 – 17.08)	
Others [a]	0.99 (0.17 – 18.78)	
cART use in visit [b]	0.24 (0.07 – 0.77)	0.47 (0.14 – 1.68)
CD4 T cell count/100 in visit [b]	0.64 (0.45 – 0.83)	0.67 (0.47 – 0.88)
Log_{10} viral load in visit [b]	1.36 (0.95 – 1.92)	
Total partner number in visit [b]	1.07 (0.34 – 3.65)	
Smoking status [b]		
Never smoker	Reference	
Current smoker	3.11 (0.98 – 11.71)	
Former smoker	1.17 (0.26 – 3.91)	
% Abnormal cells at colposcopy:		
<25	Reference	
25 – 49	1.6 (0.45 – 5.77)	
50 – 74	0.00 (0.00 – 3.94)	
>75	0.00 (0.00 – 8.09)	
Overall impression of cervix:		
Normal	0.00 (0.00 – 19.71)	
Abnormal, but no SIL	1.15 (0.11 – 24.90)	
Low grade	1.18 (0.22 – 21.74)	
High grade	Reference	

Abbreviations: CIN2, cervical intraepithelial neoplasia-2; HIV, human immunodeficiency virus; WIHS, Women's Interagency HIV Study; HR, hazard ratio; CI, confidence interval; cART, combination antiretroviral therapy; SIL, squamous intraepithelial lesion

[a] Includes Asian/Pacific Islander, Native American/Alaskan Native and Other

[b] These variables considered time-dependent in analysis

[c] Multivariate analysis includes 3 variables: CIN2 treatment, cART use, and CD4 T cell count