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Suppressive antiretroviral therapy associates with effective treatment of high-grade cervical intraepithelial neoplasia

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ART associates with effective treatment of CIN

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Abstract

Objectives: To assess if women living with HIV (WLWH) have poorer outcome after treatment of cervical intraepithelial neoplasia (CIN2+) than HIV-negative women and to identify predictors of CIN2+ treatment failure and recurrence in WLWH.

Design: Population-based cohort study with follow-up between 1983 and 2015.

Methods: The Swedish National HIV Registry, the Swedish Population Registry and the Swedish National Cervical Screening Registry were linked to identify all women in Stockholm and Gothenburg counties (Sweden) living with HIV and diagnosed with CIN2+ (n=179) sometime between 1983 and 2014. For each WLWH, two HIV-negative women resident in the same counties and matched for country of birth, diagnosed with CIN2+, were chosen as controls.Treatment failure was defined as the presence of CIN2+ at initial follow-up. Recurrence was defined as the presence of CIN1+ subsequent to an initial normal follow-up.

Results: WLWH were three times more likely to have treatment failure (odds ratio (OR) 3.7 [95% CI 2.0-6.8]) and five times more likely to recur (hazard ratio 5.0 [95% CI 2.1-11.6] than HIV-negative women. Suppressive antiretroviral therapy (ART) at time of treatment of CIN2+ was associated with reduced odds ratio of treatment failure (OR 0.3 [95% CI 0.1-0.8]). Immunosuppression (CD4 count <200 cells/μL) associated strongly with treatment failure (OR compared to CD4 count ≥500: 8.5 [95% CI 2.3-30.7]).

Conclusions: Suppressive ART is associated with effective treatment of CIN2+. Early HIV diagnosis and ART are essential for successful CIN2+ treatment.

Keywords: HIV; HPV; cervical intraepithelial lesions; excision treatment outcome; treatment failure, recurrence.

Introduction

Women living with HIV (WLWH) have a substantially higher risk of persistent high-risk Human Papillomavirus (HPV) cervical infections [1-4] and to develop cervical intraepithelial neoplasia grade 2 or worse (CIN2+) than HIV-negative women (HNW) [5-8]. In addition, treatment failure and recurrence of cervical lesions after surgical treatment of CIN2+ seem to be more common in WLWH than in HNW [9, 10]. Although a recent meta-analysis indicates that antiretroviral therapy (ART) is associated with reduction of the incidence and progression of cervical lesions [11], it is yet uncertain what role ART plays regarding outcome after treatment of CIN2+ [12-15]. Earlier studies have often been based on self-reported ART-use with no access to HIV-RNA levels as a measure of effective ART [9, 10, 12, 15]. We conducted a country of birth matched population-based cohort study with the aim of analysing: 1) if WLWH have poorer outcome after treatment of CIN2+ than HNW 2) to identify predictors of CIN2+ treatment failure and recurrence in WLWH.

Methods

Study design, participants and data sources

We used the unique national registration number (NRN) assigned to all individuals in Sweden at birth or on immigration to link the Swedish National HIV Registry and the Swedish Population Registry with the Swedish National Cervical Screening Registry.

Swedish national HIV registry (InfCareHIV)

All WLWH, born between 1942 and 1989, living in the counties of Stockholm and Gothenburg sometime between 1983 and 2014 were identified from InfCare HIV (n=1 926, Figure 1). This

registry includes >99% of Swedish residentsdiagnosed with HIV [16]. Patients are consecutively enrolled to theregistry at time of HIV diagnosis and demographic, therapeutic,and laboratory data are registered at least every six months. We extracted data regarding ART, HIV-RNA levels, CD4counts, date of HIV-diagnosis, mode of HIV-transmission and country of birth. Approximately 56% of people living with HIV in Sweden live in the counties of Stockholm and Gothenburg.

Swedish Population Registry (SPR)

All HIV-negative women, born between 1942 and 1989, living in the counties of Stockholm and Gothenburg sometime between 1983 and 2014 were identified from the SPR (n=1189 835, Figure 1). This registry contains all individuals residing in Sweden on a permanent basis. We extracted data on birth, date of immigration, emigration, and country of birth.

Swedish National Cervical Screening Registry (NKCx)

All WLWH with a diagnosis of cervical intraepithelial neoplasia grade 2, grade 3, adenocarcinoma *in situ* or cervical cancer (CIN2+) were identified from the NKCx (n=179, Figure 1). This registry includes all cervical cytology results and histopathology results in Sweden since 1993, irrespective of where screening or colposcopy has taken place [17]. For each WLWH, two HNW, living in the same counties sometime between 1983 and 2014, diagnosed with CIN2+ (n=96 727), were randomly selected and matched for country of birth (n=321, Figure 1). For some WLWH only one or no HNW from the same country of birth could be identified (see Supplemental Digital Content Table 1, http://links.lww.com/QAD/B275). Women were excluded if they had a hysterectomy performed before start of follow-up (WLWH n=3, HNW n=11) or if they had no follow-up cervical cytology or histology within one year of CIN2+

treatment (WLWH n=36, HNW n=26) (see Supplemental Digital Content Table 2, http://links.lww.com/QAD/B275). During the study period, all women living in Sweden were invited to cervical cancer screening every three (aged 23–50) to five years (aged 51–60) according to national guidelines [18]. WLWH were recommended annual screening. Both WLWH and HNW were, during the study period, recommended cervical cytology every six months the first year after treatment of CIN2+ and thereafter annually for the subsequent 25 years. Since 2010 HPV-testing has been recommended within one year of treatment of CIN2+ [18]. Colposcopy was used when indicated. All cervical cytology and histopathology reports of included women were collected up to 31st of December 2015.

Medical records

Medical record reviews were performed to elicit information on mode of treatment of CIN2+ (LLETZ: large loop excision of the transformation zone [equal to LEEP: loop electrosurgical excision procedure], laser conisation, cold knife conisation, cryotherapy or expectancy), radicality of conization (positive endocervical and/or exocervical margins), history of smoking, and nativity. Recommendation of surgical treatment of CIN2+ did not differ between WLWH and HNW during the study period [18].

Region of birth

Women were classified into six regions of birth: Sweden, Western Europe except Sweden, Eastern Europe and Central Asia, Sub-Saharan Africa, Asia and Pacific, or Latin America and Caribbean (see Supplemental Digital Content Table 1, http://links.lww.com/QAD/B275).

Final study population

One-hundred and forty WLWH and 284 HNW, born between 1942 and 1989, randomly matched for country of birth, living in the counties of Stockholm and Gothenburg sometime between 1983 and 2014, treated for histology-verified CN2+, with at least one follow-up cervical cytology/histology within one year and no hysterectomy performed before start of follow-up were included in the final study population (Figure 1).

Definition of outcomes

Treatment failure was defined as presence of CIN2+ on cervical cytology/histology at initial follow-up, within one year of treatment. In a sensitivity analysis treatment failure was defined as presence of an abnormal (atypical squamous cells of undetermined significance or worse: ASCUS+) cervical cytology/histology at initial follow-up, within one year of treatment. Women with normal cervical cytology/histology at follow-up were considered successfully treated and were included in analysis of recurrence, defined as subsequent CIN1+. These women were followed from date of first follow-up after treatment of CIN2+, until date of recurrence, or if no recurrence took place, until date of last registered cervical cytology/histology.

Statistical analysis

Continuous data was summarized as median or mean and categorical variables listed as numbers and percentages. Logistic regression analyses were used for estimating the effect of covariates associated with treatment failure in all women (HIV-status, treatment modality, grade of cervical lesion, nativity, positive surgical margins, and smoking) and in WLWH only (suppressive ART [HIV-RNA<50 copies/ml within six months of treatment of CIN2+], CD4 count within one year of treatment of CIN2+ [continuous and stratified], nadir CD4 count [continuous and stratified],

mode of HIV transmission, decade of HIV-diagnosis). All models were adjusted for age at time of treatment of CIN2+ (continuous variable) and region of birth. Cox regression analyses were used for estimating the effect of covariates associated with recurrence, with the same covariates as mentioned for the logistic regression. Schoenfeldt residual plots were used to ensure that the proportional hazards assumption was not violated. Because levels of HIV-RNA and CD4 count at time of treatment of CIN2+ are highly dependent covariates they were not used in the same model. Nadir CD4 count was adjusted for in models including HIV-RNA level or CD4 count at time of treatment of CIN2+. Suppressive ART was defined as HIV-RNA< 50 copies/mL within six months of treatment of CIN2+, but because the lower limit of detection of HIV-RNA was 500 copies/mL in Swedish laboratories until 2004 we performed a sensitivity analysis with suppressive ART defined as HIV-RNA<500 copies/mL. In a sub analysis we compared WLWH with suppressive ART to HIV-negative women and in an additional sub analysis we compared WLWH with >6 months suppressive ART at time of treatment of CIN2+ to those with <6 months suppressive ART. A p-value < 0·05 was considered statistically significant. Calculations were done using STATA 13 software.

Ethics approval

The Regional Ethics Committee in Stockholm, Sweden granted ethical approval for this study (Dnr 212/70-31/1, date of approval 15 February 2012 + 2012/1776-32, date of approval 16 October 2012 + 2015/1970-1970-32, date of approval 12 November 2015).

Results

One-hundred and forty WLWH and 284 HNW were included in the final study population. Mean age was slightly above 30 (Table 1). About 70% were migrants, of whom a majority was born in

Sub-Saharan Africa. Most WLWH had acquired HIV heterosexually (86%) and a majority had at one point been highly immunosuppressed (median nadir CD4 count 147 cells/μL [IQR 56-360], Table 3). Sixty-five % were on at least three antiretrovirals at time of treatment of CIN2+ and 53% on suppressive ART.

Treatment failure defined as CIN2+, in all women

Among all participants, 30 (21%) WLWH and 20 (7%) HNW had treatment failure (Table 1). WLWH were more than three times more likely to have a treatment failure (OR 3.7 [95% CI 2.0-6.8], Table 2) than HNW. When restricting WLWH to those with suppressive ART at time of treatment of CIN2+ (n=75), the association decreased and was no longer statistically significant (OR 1.8, [95% CI 0.8-4.2]). Grade of lesion was significantly associated with treatment failure in WLWH only (Table 2). Treatment modality and nativity was not significantly associated with treatment failure in logistic regression analysis (Table 2). We were not able to adjust for smoking due to lack of adequate registration in medical records of this variable. Positive surgical endo/exo-cervical margins at time of treatment were also inadequately registered in medical records.

Treatment failure defined as CIN2+, in WLWH only

Suppressive ART (HIV-RNA< 50 copies/mL) was associated with reduced odds ratio of treatment failure (OR 0.3 [95% CI 0.1-0.8]) and the association remained after adjusting for nadir CD4 count (Table 2). When re-defining suppressive ART as HIV-RNA< 500 copies/mL the results were similar (OR 0.3 [95% CI 0.1-0.7]). When restricting the analysis to WLWH with suppressive ART at time of treatment of CIN2+ there was no association between time on suppressive ART (more or less than six months) and treatment failure (OR 1.1 [95% CI 0.3-

5.3]). There were only 9 cases of treatment failure among women with suppressive ART at time of treatment of CIN2+. Advanced immunosuppression (CD4 count <200 cells/μL) at time of treatment of CIN2+ was associated with more than eight times higher odds ratio of treatment failure than a CD4 count ≥500 cells/μL (OR 8.5 [95% CI 2.3-30.7], Table 2). Although treatment failure was associated with low median nadir CD4 count in univariate analysis (Table 3), CD4 nadir <200 was not significantly associated with higher odds ratio of treatment failure compared with nadir CD4 count ≥350 cells/μL (OR 6.5 [95% CI 0.8-53.6]) in multivariate analysis and the association decreased even more when adjusting for CD4 count at time of treatment in the same model (Table 2). Earlier decade of HIV-transmission was associated with treatment failure in univariate (Table 3) but not in multivariate analysis (Table 2). Mode of HIV transmission was not significantly associated with treatment failure (Table 2).

In sensitivity analysis treatment failure was defined as ASCUS or worse. This brought similar results as treatment failure defined as CIN2+ (see Supplemental Digital Content Table 3, http://links.lww.com/QAD/B275).

Recurrence

A total of 304 women (77 WLWH and 227 HNW) had a normal cervical cytology/histology at follow-up and were included in analysis of recurrence. The study included 1912 person years (pys) (418 pys vs. 1494 pys for WLWH and HNW, respectively) with median time of follow-up of 3.9 (IQR 1.1-7.4) vs. 4.2 (IQR 1.3-10.7) years for WLWH and HNW respectively (Table 1). WLWH were five times more likely to recur (HR 5.0 [95% CI 2.1-11.6], Supplemental Digital Content Table 3, http://links.lww.com/QAD/B275). Crude HR was similar to adjusted HR (crude HR 4.6 [95% 2.0-10.6]. When restricting WLWH to those with suppressive ART at time of

treatment of CIN2+ (n=49), these women had remaining higher risk of recurrence compared to HNW (HR 4.7 [95% CI 1.6-14.4]). Treatment modality or grade of lesion at time of treatment was not significantly associated with recurrence (Supplemental Digital Content Table 3, http://links.lww.com/QAD/B275). We were not able to adjust for nativity due to few outcomes and lack of complete data for this variable.

Recurrence, in WLWH only

Of 77 WLWH included in analysis of recurrence, 49 (64%) had suppressive ART at time of treatment of CIN2+ and a high median CD4 count 440 cells/μL (IQR 307- 570). Only 13 WLWH were defined as having had recurrence (Table 1) of whom six (46%) had suppressive ART at time of treatment of CIN2+ and ten (77%) at time of recurrence-diagnosis. Suppressive ART was not significantly associated with reduced risk of recurrence (HR 1.0 [95% CI 0.3-3.4], Supplemental Digital Content Table 3, http://links.lww.com/QAD/B275). CD4count (continuous, cells/μL) at time of treatment of CIN2+ was associated with recurrence (p_{trend}=0.0347) but CD4count <200 cells/μLat time of treatment was not significantly associated with a higher risk of recurrence than CD4count ≥500 cells/ μL (HR 8.2 [95% CI 0.8-79.3]) and neither was nadir CD4count <200 compared to ≥350 cells/μL (HR 1.8 [95% CI 0.2-14.3], Supplemental Digital Content Table 3, http://links.lww.com/QAD/B275). A later HIV-diagnosis (2004-2013; n=28) was associated with an increased risk of recurrence compared to an early (1983-1993; n=23) (HR 8.1 [95% CI 1.0-64.9]) but there were only two more events among those diagnosed with HIV between 2004-2013 (n=5) compared to 1983-1993 (n=3). Mode of HIV transmission was not significantly associated with treatment failure (Supplemental Digital Content Table 3, http://links.lww.com/QAD/B275).

Discussion

In our comprehensive, population-based cohort study with essentially complete follow-up, women living with HIV had more treatment failure and recurrence, after treatment of CIN2+, than HIV-negative women. Suppressive ART and CD4 counts above 499 at time of treatment of CIN2+ were associated with effective treatment of CIN2+. Additionally, CD4 count at time of treatment of CIN2+ seems to be a better predictor of treatment success than nadir CD4 count.

Suppressive ART was associated with effective treatment of CIN2+. A majority of studies using only self-reported use of ART as a measure of effective ART have not found an association between ART and successful treatment [9, 10, 12]. In an early smaller study, Robinson et al. found less recurrence (in our study defined as treatment failure) in WLWH on self-reported ART compared to those without, although there was no measure of effect analysis in that study [15]. Reimers et al. did not find an association between HIV-RNA levels and treatment failure [13]. Contrary to our study, both these studies included women treated for CIN1 despite the fact that this is usually a self-healing lesion.

Similar to earlier studies, severe immunosuppression at time of treatment of CIN2+ was associated with treatment failure [9, 10, 13, 19]. A low nadir CD4 count was not as robustly associated with treatment failure as CD4 count measured at time of treatment. When adjusting for CD4 count and nadir CD4 count in the same model the association between nadir CD4 count and treatment failure decreased even more. This may indicate that CD4 count at time of treatment of CIN2+ is a better predictor of treatment failure than nadir CD4 count.

Our population based study found more high-grade lesions at time of treatment failure than in a closely followed US prospective cohort [10], but less than in another US study that included more severely immunosuppressed women and fewer on suppressive ART [13]. It has been suggested that failure after CIN2+ treatment in WLWH mainly represents low-grade lesions due to opportunistic HPV-infections [10], but this is not supported in our study where treatment failure was high even when restricted to CIN2+.

In agreement with earlier studies WLWH in our study had more treatment failure than HNW [9, 10, 19]. Although grade of initial lesion was significantly associated with treatment failure only for WLWH this does not explain our results as differences depending on HIV-status remained after adjusting for grade of lesion. Even WLWH with suppressive ART had remaining, though non-significant, higher odds of having a treatment failure, than HNW, which may be due to residual chronic immune activation and lack of full restoration of cervical mucosal immunity despite successful inhibition of HIV replication [11, 20].

WLWH had higher risk of recurrence than HNW and the risk of recurrence increased with diminishing CD4 count at time of treatment of CIN2+. It is difficult to compare our results to those from earlier studies since recurrence has often been unclearly defined, more specifically it was often not specified if a normal cytology/histology was found at first follow-up after treatment before inclusion in analysis of recurrence [14, 19, 21]. One US study with access to HIV-RNA levels found an association between high HIV-RNA-levels and an increased risk of recurrence [13] while studies using self-reported ART have found conflicting results [10, 22]. We did not find suppressive ART to be associated with a reduced risk of recurrence, which may have been due to few events in WLWH (n=13) leading to a lack of precision of this estimate.

Limitations of our study include the inability to adjust for smoking due to inadequate registration of this variable in medical records. Even though smoking is a known risk factor of treatment failure it is unlikely that confounding by smoking entirely explain our results. Registration of positive surgical margins was also often lacking in medical records in our study. This is also a known risk factor of treatment failure and recurrence and WLWH have been shown to have positive margins more often than HNW [22, 23]. However, as positive margins are most probably in the causal pathway between immunosuppression and treatment failure (i.e. an intermediate variable) it would not have been correct to adjust for positive margins. We did not have access to HPV status at time of treatment of CIN2+ or at time of treatment failure/recurrence as this has only lately been registered in the screening registry. We did not have access to mode of treatment of CIN2+ for all women, because of lack of information in medical records, therefore more women than stated may have been treated with expectancy only. Traditionally WLWH are prone to more aggressive treatment of cervical lesions than HNW so if anything, this may have led to an underestimation of the odds of treatment failure and risk of recurrence in WLWH. Despite these limitations, our study has several strengths. We have had access to individual data from essentially complete national HIV registry and nationwide registry of cervical cytology and histopathology reports with long-term follow-up, altogether providing high validity.

Conclusions

To our knowledge, this is the first study showing an association between suppressive ART and successful treatment of CIN2+ in WLWH. In countries where the burden of HIV is high and access to regular cervical cancer screening, HPV vaccination and treatment of CIN2+ is poor it is

especially important with early HIV diagnosis, access to ART, and continuum of care to reach successful CIN2+ treatment.

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CC, PW, JD, AS and PS contributed to the study design. CC, AvB and PS acquired the data. CC obtained funding. CC and PW performed the statistical analysis. CC drafted the manuscript. All authors contributed to the interpretation of the data, critically reviewed the manuscript and approved the final version of the report.

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Table 1.Characteristics of participants.

	WLWH	HIV-negative
All, n	140	284
Age, years, mean (SD)		
	34 (8)	32 (8)
Region of birth[1], n (%)		
Sweden	38 (27)	95 (33)
Sub-Saharan Africa	65 (46)	112 (39)
Asia and Pacific	26 (19)	53 (19)
Eastern Europe & Central Asia	6 (4)	12 (4)
Latin America & Caribbean	2 (1)	5 (2)
Western Europe except Sweden	3 (2)	7 (2)
Number of births, median (IQR)		
	1 (0-2)	1 (0-2)
Lesion grade, n (%)		
CIN2	81 (58)	149 (52)

CIN3	58 (41)	132 (46)
AIS	1 (1)	3 (1)
Treatment modality, n (%)		
LLETZ	77 (55)	97 (34)
laser conization	7 (5)	32 (11)
cold knife conization	1 (1)	1 (0.3)
unspecified excision/conization	23 (16)	65 (23)
cryotherapy	2 (1)	4 (1)
missing/unclear	30 (21)	84 (30)
expectancy	-	1 (0.3)
Time to first follow-up, years, median (IQR)		
	0.6 (0.4-0.8)	0,5 (0.3-0.6)
Treatment failure, n (%)		
Defined as ASCUS+	63 (45)	57 (20)
Defined as CIN2+	30 (21)	20 (7)
Grade of treatment failure lesion, n (%)		

ASCUS	7 (5)	12 (4)
CIN1	26 (19)	25 (9)
CIN2	16 (11)	14 (5)
CIN3	14 (10)	6 (2)
Recurrence[2], n/N (%)		
	13/77 (17)	10/227 (4)
Time of follow-up, years, median (IQR)		
	3.9 (1.1-7.4)	4.2 (1.3-10.7)
Grade of recurrence lesion, n/N (%)		
CIN1	8/13 (62)	5/10 (50)
CIN2	3/13 (23)	3/10 (30)
CIN3	2/13 (15)	2/10 (20)

Measurements closest to date of treatment of CIN2+, unless otherwise stated. Data are number (%) or median (IQR), unless otherwise indicated. Percentages do not always add up to hundred due to rounding. [1] See supplemental Digital Content Table 1, http://links.lww.com/QAD/B275.[2] Recurrence defined as the presence of CIN1+ subsequent to an initial normal follow-up.Abbreviations: ASCUS: atypical squamous cells of undetermined significance; ASCUS+: ASCUS or worse; AIS: adenocarcinoma in situ; CIN: cervical intraepithelial neoplasia; CIN2+;

CIN grade 2 or worse; LLETZ: large loop excision of the transformation zone; WLWH: women living with human immunodeficiency virus.

Table 2. Characteristics associated with treatment failure defined as CIN2+ at time of first follow-up. Estimated through odds ratios and their corresponding 95% CIs in women living with HIV compared with HIV-negative women and within the HIV-infected subpopulation.

CIN2+ at follow-up[1]	Odds ratio (95% CI)
HIV+ vs. HIV-negative	3.7 (2.0-6.8)
HIV+ vs. HIV-negative, adjusted for grade of initial lesion	3.9 (2.1-7.2)
HIV+ with suppressive ART[2] vs. HIV-negative	1.8 (0.8-4.2)
Only HIV+ women	
Suppressive antiretroviral therapy	
Suppressive ART (defined as HIV-RNA<50) vs. HIV-RNA >50 copies/ml	0.3 (0.1-0.8)
Suppressive ART (defined as HIV-RNA<500) vs. HIV-RNA>500 copies/ml	0.3 (0.1-0.7)
Suppressive ART vs. HIV-RNA >50, adjusted for nadir CD4 count	0.3 (0.1-0.7)
Suppressive ART >6 months vs. <6 months[3]	1.1 (0.3-5.3)
Suppressive ART >6 months vs. <6 months, adjusted for nadir CD4 count	1.1 (0.2-5.1)
CD4 count, cells/μL[4]	

<200	8.5 (2.3-30.7)
200-349	0.9 (0.2-4.0)
350-499	1.3 (0.3-5.1)
≥500	1 (ref)
Nadir CD4 count, cells/μL[5]	
<200	6.5 (0.8-53.6)
200-349	2.7 (0.3-26.0)
≥350	1 (ref)
Nadir CD4 count <200 compared to ≥350, adjusted for CD4 count (cont.)	2.9 (0.3-27.9)
Year of HIV diagnosis	
1984-1993	1(ref)
1994-2003	0.5 (0.2-1.3)
2004-2013	0.4 (0.1-1.2)
Mode of HIV transmission	
Heterosexual	1(ref)
Intravenous drug use	1.0 (0.2-4.1)

Other/unknown	0.8 (0.1-7.3)
Number of births	
0	1(ref)
≥1	0.5 (0.2-1.6)
Lesion grade at time of treatment	
CIN2	1(ref)
CIN3	3.0 (1.3-7.0)
Treatment modality	
LLETZ	1(ref)
Other/missing[6]	1.2 (0.5-2.8)
Only HIV negative women	
Number of births	
0	1(ref)
≥1	2.9 (0.3-27.0)
Lesion grade at time of treatment	
CIN2	1(ref)

CIN3	1.0 (0.4-2.6)
Treatment modality	
LLETZ	1(ref)
Laser conization	1.0 (0.2-5.2)
Other/missing[7]	1.3 (0.5-3.6)

All models are controlled for age and Region of birth. [1]Defined as cervical intraepithelial neoplasia grade 2, grade 3 adenocarcinoma in situ and invasive cervical cancer. [2]Defined as HIV-RNA<50 copies/ml within six months of treatment of CIN2+, unless otherwise stated. [3]More or less than six months of suppressive ART at time of treatment of CIN2+.[4]Within one year of treatment of CIN2+.[5]Lowest CD4cell count measured since HIV was diagnosed. [6]Defined as laser conisation, cold knife conisation, unspecified excision/conization, cryptherapy, missing/unclear and expectancy.[7]Defined as cold knife conisation, unspecified excision/conization, cryptherapy, missing/unclear and expectancy. Abbreviations: ART: antiretroviral therapy; CIN2+: cervical intraepithelial neoplasia grade 2, grade 3 adenocarcinoma in situ and invasive cervical cancer; HIV+: HIV infected; LLETZ: large loop excision of the transformation zone

Table 3. Characteristics of women living with HIV at time of treatment of CIN2+, with or without a subsequent treatment failure defined as CIN2+.

Treatment failure	**No**	**Yes**[1]	p-value[2]
All, n	110	30	
Age, mean (SD)			
	33 (6)	36 (8)	0,1275
Region of Birth[3], n %)			0,1552
Sweden	27(25)	11 (37)	
Sub-Saharan Africa	50 (45)	15 (50)	
Asia & Pacific	24 (22)	2 (7)	
Eastern Europe & Central Asia	5 (4)	1 (3)	
Latin America & Caribbean	2 (2)	-	
Western Europe except Sweden	2 (2)	1 (3)	
Number of births, median (IQR)			
	1 (0-2)	1 (0-3)	0.8211
Antiretroviral therapy, n (%)			0.5896
On at least three ARTs	79 (72)	13 (43)	

On two ARTs	2 (2)	5 (17)	
On one ART	5 (5)	1(3)	
No ART	24 (21)	11(37)	
Suppressive antiretroviral therapy			
HIV-RNA<50 copies/mL[4] , n (%)	66 (60)	9 (30)	0,0033
Level of immunosuppression			
CD4 count, cells per µL, median (IQR)[5]	385 (270-520)	186 (120-430)	0,0014
CD4 strata, cells per µL, n (%)			0,0014
<200	14 (13)	16 (53)	
200-349	32 (29)	4 (13)	
350-499	33 (30)	6 (20)	
≥500	31 (28)	4 (13)	
CD4nadir, cells per µL, median (IQR)[6]	179 (80-258)	80 (30-161)	0,0111
CD4nadir strata, cells per µL, n (%)			0,2766
<200	65 (59)	24 (80)	
200-349	30 (27)	5 (17)	

350-499	13 (12)	-	
≥500	2 (2)	1 (3)	
Year of HIV diagnosis, n (%)			0.0223
1984-1993	31 (27)	14 (45)	
1994-2003	39 (36)	9 (31)	
2004-2013	40 (37)	7 (24)	
Mode of HIV transmission, n (%)			0.8064
Heterosexual	94 (85)	26 (87)	
Intravenous drug use	11 (10)	3 (10)	
Other/unknown[7]	5 (5)	1 (3)	
Lesion grade at follow-up, n (%)			N/A
CIN2	-	16 (53)	
CIN3	-	14 (47)	
Lesion grade at time of treatment, n (%)			0.0227
CIN2	69 (63)	12 (40)	
CIN3	40 (36)	28 (60)	

AIS	1 (1)	-	
Treatment modality, n (%)			0.8241
LEETZ	62 (56)	15 (50)	
laser conization	7 (6)	-	
cold knife conization	1 (1)	-	
unspecified conization/excision	20 (18)	3 (10)	
cryotherapy	-	2 (7)	
Missing/unclear	20 (18)	10 (33)	

Measurements closest to date of treatment of CIN2+, unless otherwise stated. Data are number (%) or median (IQR), unless otherwise indicated. Percentages do not always add up to hundred due to rounding. [1] Defined as cervical intraepithelial grade 2, grade 3/ adenocarcinoma in situ and invasive cervical cancer. [2] P-values acquired through logistic regression analysis, univariate analysis. [3]See supplemental Digital Content Table 1, http://links.lww.com/QAD/B275. [4]Within six months of treatment of CIN2+.[5]Within one year of treatment of CIN2+.[6]Lowest CD4count measured since HIV was diagnosed. [7]Defined as bloodproducts, homo/bisexual and unknown.

Abbreviations: AIS: adenocarcinoma in situ; ART: antiretroviral therapy; CIN: cervical intraepithelial neoplasia; LEETZ: large loop excision of the transformation zone; N/A: non applicable; WLWH: women living with human immunodeficiency virus.

Figure 1. Flowchart of the selection of the study population.