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Incidence and progression of cervical lesions in women with HIV: A systematic global review

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Summary

Objective—Global data on cervical lesion incidence and progression in HIV-positive is essential for understanding the natural history of cervical neoplasia and informing screening policy.

Methods—A systematic review was performed summarizing the incidence and progression of cervical lesions in HIV-positive women.

Results—Of 5,882 HIV-positive women from 15 studies, incidence ranged from 4.9 to 21.1 cases per 100 woman-years for any cervical lesion and 0.4 to 8.8 cases per 100 woman-years for high grade cervical lesions. HIV-positive women showed a median 3-fold higher incidence of cervical lesions compared to HIV-negative women. Of 1,099 HIV-positive women from 11 studies, progression from low to high grade lesions ranged from 1.2 to 26.2 cases per 100 woman-years. Both incidence and progression rates increased with lower CD4 counts. The effect of antiretroviral therapy on the natural history of cervical neoplasia remains unclear.

Conclusions—HIV-positive women have higher incidence and progression of cervical neoplasia. Cervical cancer screening should be integrated into HIV treatment programs.

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SD performed the literature search, extracted data, and prepared the manuscript. AR helped with manuscript preparation, contributed subject matter expertise, edited and reviewed the manuscript. CF provided subject matter expertise, edited and reviewed the manuscript. JT checked the data extraction, edited and reviewed the manuscript. JS provided subject matter expertise, edited and reviewed the manuscript.

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Keywords

cervical cancer; cervical lesions; HIV; incidence; progression

Introduction

In 2008, an estimated 33 million people were HIV infected worldwide, with 2.7 million newly acquired HIV infections, most of which occurred in less developed countries¹. HIV prevalence continues to rise due to both the high rate of new infections and the beneficial increase in life expectancy from antiretroviral therapy (ART). HIV is increasingly becoming a disease of women, with almost 50% of prevalent cases occurring in females¹. This trend is particularly noticeable in sub-Saharan Africa where females have approximately three times the HIV prevalence of males¹.

Many resource limited nations that have high HIV prevalence also have high rates of cervical cancer because of limitations of screening and treatment. Cervical cancer is caused by infection with carcinogenic HPV genotypes² and HIV infection is strongly associated with a higher prevalence, incidence, and persistence of human papillomavirus (HPV) infection³⁻⁶. Women with HIV have a higher prevalence of cervical squamous epithelial lesions (SIL) and invasive cervical cancer⁷⁻¹³. Recognizing this connection, the CDC declared invasive cervical cancer as an AIDS-defining illness in 1993¹⁴. Additionally, reducing cervical cancer in HIV-positive women is a primary focus of a joint public-private international initiative launched in 2011, the Pink Ribbon Red Ribbon initiative¹⁵.

The large number of women living with HIV underscores the need to better understand the natural history of cervical precancer and cancer development in this high-risk population. While reports have linked HIV-related immunosuppression with an increased incidence of cervical precancer lesions and invasive cervical cancer^{3,16}, there is no global review compiling data on rates of incidence and progression of cervical neoplasia in HIV-positive women. Thus, we systematically reviewed the current literature on cervical precancer and cancer among HIV-positive women worldwide and examine important factors related to immunosuppression, including CD4+ T-cell count and ART use.

Methods

In order to identify studies related to cervical lesion incidence, a systematic literature search was conducted in MEDLINE for all studies indexed through January 31, 2012 with no specified start date using the following search terms: (uterine cervical neoplasms (MeSH term) OR pap abnormality OR squamous intraepithelial lesions) AND cohort studies (MeSH term) limited to AIDS (keyword for HIV-related studies). Articles written in languages other than English were translated and reviewed for inclusion criteria. References of identified publications were also used to identify additional published articles for review. For cervical lesion incidence, studies were included if: i) the study sample included 20 or more HIV-positive women; ii) a cohort design was used to assess incidence of SIL or greater and/or cervical intraepithelial neoplasia (CIN)1 or greater; and iii) study participants had normal

cervical screen at baseline. Where possible, incidence rates were split for high grade versus low grade SIL and CIN (HSIL/CIN2–3 and LSIL/CIN1, respectively).

Articles reporting on cervical lesion progression were selected from the chosen incidence articles as well as through a separate MEDLINE search. The MEDLINE search was conducted for all studies indexed by January 12, 2012 using the following search terms: uterine cervical neoplasms (MeSH term) AND progression limited to AIDS (which limits the search to HIV-specific publications). Studies were included in the progression analysis if: i) the study sample included 20 or more HIV-positive women; ii) a cohort design was used to estimate progression to SIL or greater and/or CIN1 or greater; and iii) study participants had atypical cells of unknown significance (ASCUS), low-grade SIL (LSIL), or low-grade CIN (CIN1) diagnosis at baseline.

Incidence and progression rates were reported as stated in the articles or estimated from reported number of cases, subjects and median or mean follow-up time. Additionally, study cumulative risks of incidence and of progression were reported. Risk ratios were reported as stated in the articles or estimated using the ratio of the study cumulative risks. In this review, the term ART is broadly used to mean any ART use (monotherapy or greater). However, in the tables and results, ART and highly active antiretroviral therapy (HAART) were labeled as written in the individual articles with ART typically referring to monotherapy or dual therapy and HAART referring to triple therapy or greater. When the study included both women using ART and HAART, the term “mixed ART” is applied. When more than one article based on the same study population met the selection criteria for inclusion, the article with the largest number of women was used, unless multiple articles could contribute to separate analyses.

Results

Incidence of cervical lesions

From 451 screened abstracts, our search identified 15 cohort studies presenting data on the incidence of cervical neoplasia with observational data on 5882 HIV-positive women in total (Table 1). Most studies were conducted in the European Union (N=7; 47%)^{7,17–22}, with 1 including women from France and French Guiana¹⁰, and 1 including women from Europe and South Africa²³. Three studies were conducted in the United States^{24–26}, 2 were conducted solely in Africa^{27,28}, and 1 took place in Thailand²⁹. No studies came from Australia, Central America, or Eastern Europe. Study populations were primarily from health clinics, sexually transmitted disease clinics, and drug treatment centers. Less than half of the studies (N=6, 40%) had both HIV-positive and HIV-negative populations. Median age of study participants ranged from 29 to 43, with most studies having a median age in the low 30s. The number of participants with follow-up data in the included studies ranged from 27 to 1,931 HIV-positive women; most had 100 or more HIV-positive study participants. Study lengths ranged from less than a year to 8 years, with most studies reporting follow-up visits every six months. In 2 of the studies, all study participants were receiving HAART^{21,30}. Eleven of the studies had a proportion of the participants receiving ART (3 ART, 3 HAART, and 5 mixed HAART/ART)^{7,10,18,19,22–26,28,29}, 1 study had no participants receiving ART²⁷, and 1 study did not specify ART use²⁰.

Cervical lesions were identified through cytology in all of the studies, with 8 confirming some or all diagnoses with histology. Incidence rates of any SIL for HIV-positive women who had normal cytology at study entry ranged from 4.9 to 21.1 cases per 100 women-years (Table 1). In all studies that included HIV-negative populations (N=6, 40%), the incidence rate of any SIL was greater in HIV-positive than HIV-negative participants, with a median 3-fold increase in incidence (range 1.5 – 10.0). Incidence rates of LSIL ranged from 2.0 to 16.2 cases per 100 women years (Table 1 and Figure 1). Rates of HSIL/CIN2–3 for HIV-positive women varied from 0.4 to 8.8 cases per 100 women-years. Studies with both HIV-positive and HIV-negative populations showed higher rates of HSIL/CIN2–3 for HIV-positive participants. As an additional measure, study cumulative incidence of LSIL and of HSIL, though not comparable between studies as study length was variable, also consistently showed higher risk for HIV-positive participants than for HIV-negative participants within the same study.

Incidence stratified by CD4 counts and antiretroviral use

Seven studies included analysis of lesion incidence by CD4 count categories (Table 2) ^{7,10,18,19,21,26,27}. As the studies varied in length of follow-up, and varied in the categorization of CD4 counts, comparisons of cumulative incidence between studies were not meaningful. Within study comparisons, however, show that in 6 studies, lower CD4 count was associated with an increased incidence of abnormal cervical cytology ^{7,10,19,21,26,27}, although most estimates were not statistically significant. Two studies assessed nadir CD4 counts and reported no statistically significant relationship with incidence ^{29,31}.

Five studies presented risk ratios for SIL incidence by ART use (Table 3) ^{19,22,26,31,32}. Of the 4 studies that reported on HAART use specifically ^{22,26,31,32}, 2 studies found a reduced incidence and 2 studies found an increased incidence of SIL for users of HAART. However, only 1 of these estimates, finding reduced incidence, was statistically significant ²². Two studies reported on ART use, with one reporting a decrease and 1 reporting an increase in incidence of SIL ^{19,26}. Again, only one study, finding increased incidence, found this association to be statistically significant ²⁶.

Progression of low grade lesions

From 219 screened abstracts, our search for cervical lesion progression studies in HIV-positive women identified 11 cohort studies, including data from 1099 HIV-positive women in total (Table 4). Four of the studies were conducted in the USA ^{33–36}, 4 in the European Union with one including women from France and French Guiana ^{7,10,37,38}, 2 in Africa ^{28,39}, and 1 in Brazil. No studies came from Asia, Australia, Central America, or Eastern Europe. Half of the studies (N=5, 45%) had both HIV-positive and HIV-negative populations. Median age of study participants ranged from 27 to 38, with the majority of studies having a median age in the low 30s. Eight of the studies reported a proportion of the participants receiving ART (2 ART, 1 HAART, and 5 mixed ART/HAART) ^{7,10,28,33–36,38}. In 3 studies ART use was not specified ^{37,39,40}. In none of the study populations were all participants receiving ART. The number of participants ranged from 28 to 242 HIV-positive women, with most having fewer than 100 participants. Study lengths ranged from one year to 7

years, with the majority reporting follow-up visits every six months. To assess the grade of cervical lesions, most studies used cytology, with 6 studies (56%) confirming some or all diagnoses with histology.

Cervical lesion progression rates from LSIL/CIN1 to greater than LSIL/CIN1 (most commonly HSIL/CIN2–3) for HIV-positive women ranged from 1.2 to 26.2 cases per 100 women-years. Two studies followed women with ASCUS at baseline^{33,34}, finding a rate of 13.7 cases of SIL per 100 women-years and 3.2 cases of HSIL per 100 women-years. Study cumulative risks, though not comparable between studies, were higher for HIV-positive participants than for HIV-negative participants in all five studies that included both populations^{10,33,35,37,39}.

Progression of lesions stratified by CD4 counts

Three studies reported progression of cervical lesions separated by CD4 count categories (Table 5)^{10,33,37}. The cumulative risks of progression in the studies presenting these data appeared to show a trend of increased risk of progression with decreasing CD4 count^{10,37}. Risk ratios for progression were higher with lower CD4 count^{33,37}, however only 1 of the studies reported statistical significance for this association. Nadir CD4 count was not evaluated. None of the studies clearly delineated progression risk for ART users versus non-users.

Discussion

Our comprehensive search identified 15 studies reporting incident cervical lesions and 11 studies reporting progression of cervical lesions for HIV-positive women. These studies showed a wide range of incidence and progression rates for cervical lesions in HIV-positive populations. In studies with both HIV-positive and HIV-negative populations, the incidence rate of cervical lesions was a median three-fold higher in HIV-positive women as compared to HIV-negative study participants. HIV-positive women were also at least twice as likely to have cervical lesions that progressed in severity as compared to HIV-negative women. The majority of studies showed that lower CD4 counts were associated with increased incidence and progression of cervical lesions in HIV-positive women, however, this relationship was usually not statistically significant, often due to small sample size per strata of CD4 counts.

The evidence on ART use and cervical lesion incidence was more inconsistent. Though one study showed a reduction in incidence with HAART use versus non-HAART use²², most studies found no significant difference between HAART/ART use and non-use^{19,26,31,32}. Associations may be confounded by the practice of initiating ART use only in patients with low CD4 counts or lack comparability due to differences in CD4 count recovery, HIV viremia, and follow-up time after ART initiation. Additionally, ART treatment has evolved since its introduction so it is important to note that many of the study populations that received ART were receiving single or dual drugs as compared to current standard of triple drug combinations (HAART) currently in practice. Life expectancy of HIV-positive individuals on HAART is also increasing and thus a greater number of HIV-positive women may be susceptible to cervical cancer and associated diseases in the future. In addition, an important gap in the literature is the effect of HAART use and progression of cervical

lesions. Minkoff et al. (2010) found a significant increase in clearance of SILs among adherent women on HAART (adjusted odds ratio 2.4; 95% confidence interval 1.1–5.2) as compared to pre-HAART³². Two more recent studies, published after the cut off for this analysis, also found a reduction in progression or increase in regression for consistent users of HAART^{41,42}. The relationship of HAART use and progression may become more defined when additional analyses are done in cohorts of women only on HAART and when HAART adherence and effectiveness are considered.

As both HIV and HPV are sexually transmitted infections, the increase in cervical lesions found in HIV-positive women may be due to shared behavioral risk factors such as high number of sexual partners or high risk sexual partners. However, biological mechanisms have also been implicated. The increased risk of cervical lesion development and progression seen in women with HIV is postulated to be due to both an impaired immune system and an increased potential for unregulated cell growth. For example, cervical molecular profiles of HIV-positive women show alterations in oncogenic and immunogenic protein expression^{43–45}. Additionally, there is evidence linking the HIV-1 transactivator protein (Tat) with increased expression of HPV oncogenes and proliferation of HPV-infected cells⁴⁶. Together these data indicate an altered immune response to HPV infection and an altered natural history of cervical cancer in HIV-positive women. In alignment with the hypothesis that impaired immune function reduces the ability to clear HPV infection, thus increasing the probability of developing cervical precancer and cancer, most studies found an inverse association between level of immunosuppression, as indicated by CD4 counts, and the incidence and progression of cervical lesions^{7,10,19,21,26,27,33,37}.

Our review is limited, however, by the small number of studies reporting rates for cervical lesion incidence and progression, making between-study comparisons difficult. Where possible, rates were approximated based on median follow-up time. This review identified gaps in the literature on incidence and progression of cervical precancer in HIV-positive women. Most studies had a median age for study participants in the low 30s; few studies reported on older populations. Given the increased life expectancy of HIV-positive women due to HAART, assessment of this growing demographic of women 30 years and older is needed. Additionally, HIV viral load was not systematically extracted in this analysis due to the general lack of consistent data throughout the studies. Also, we did not find studies meeting our criteria that addressed the effects of HAART use on progression risk from low-grade lesions. A recent large study, which was not included in our literature review, reported that HAART use reduced the rate of cervical lesion progression from LSIL (rate ratio 0.52 for HAART users versus ART non-users)⁴¹. HAART use has also been associated with a reduction in the combined rate for incidence and progression of cervical neoplasia (rate of any progression from normal or LSIL baseline), though not always reaching statistical significance^{28,41,47–49}. Additionally, evidence shows that HAART use increases the rate of regression of precancerous lesions^{32,50,51}.

The compiled research highlights the high risk of cervical precancer development and progression in HIV-positive women. This risk appears to be greater in women with reduced immune function but more evidence is needed to determine how HAART use modifies risk of incidence and progression. Our findings reinforce the importance of screening for cervical

lesions in HIV-positive populations, particularly those with lower CD4 counts that are at a higher risk for both incident and progressive cervical disease outcomes. Given the healthcare resources focused on HIV care, integrating cervical screening with HIV treatment programs is essential to reduce untimely death of women from this preventable cancer.

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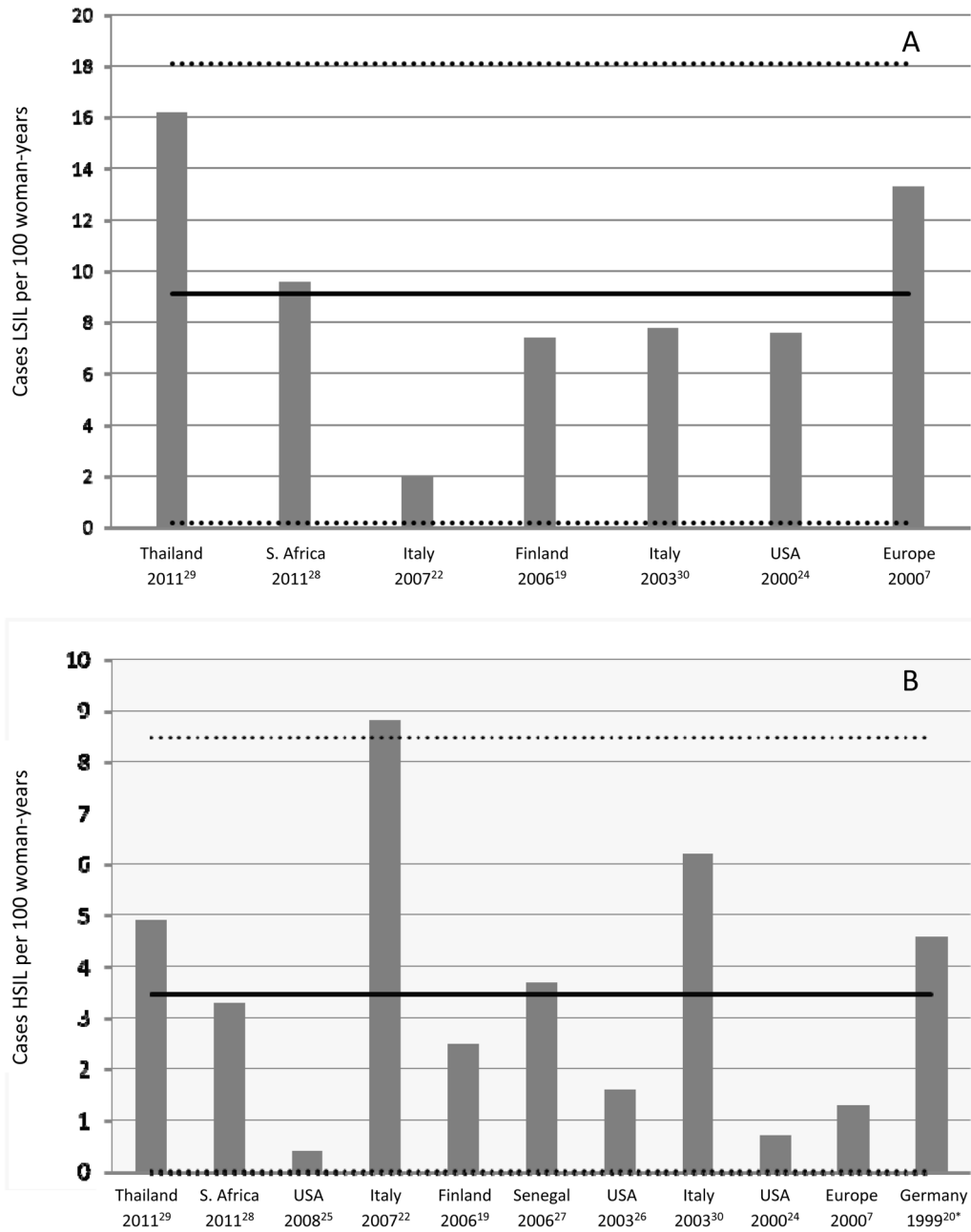


Figure 1. Incidence rates reported or calculated for LSIL (A) or HSIL (B) in HIV-positive women. Rates are reported as cases per 100 woman-years. Solid lines show unweighted mean rate. Dotted lines show 95% confidence intervals around the unweighted mean. *This study reports CIN2–3.

Table 1

Incidence rate estimates of cervical neoplasia from HIV-positive populations

Author/year Country Study Population	Median (mean) age, years	ART use	Women with follow-up data (N)	Median (mean) follow- up time, months	Assessment method (intervals)	Baseline	Outcome	Cases (N)	Cases /100 woman-years	Study cumulative risk
Chalermchockcharoenkit et al. 2011 ²⁹ Thailand STD clinic 2004–2009	HIV+ (30)	mixed*	HIV+ 444	HIV+ 10	cytology [†] (6 months)	normal	LSIL	HIV+ 60	HIV+16.2 [‡]	HIV+ 14%
Omar et al. 2011 ²⁸ South Africa HIV wellness clinic 2003–2009	HIV+ 32	mixed*	HIV+ 832	HIV+ 30	cytology(6–12 months)	normal	LSIL	HIV+ 183	HIV+ 9.6	HIV+ 22%
Massad et al. 2008 ²⁵ USA Women's Interagency HIV Study (WIHS) university, public, and private medical centers and clinics 1994–2006	HIV+/- 43 [§] //	mixed [¶]	HIV+ 1931// HIV- 533//	HIV+/- 101 [§] //	cytology (6 months)	normal	HSIL	NS	HIV+ 0.4 HIV- 0.1	HIV+ 4% HIV- 1%
Kitchener et al. 2007 ²³ 5 European nations and South Africa Hospital and community health Centers 2000–2004	HIV+ 33//	mixed*	HIV+ 552	HIV+ 30//	cytology (6 months)	normal	SIL	HIV+ 117	HIV+ 8.5	HIV+ 21%
Sirera et al. 2007 ²¹ Germany University HIV clinic 1997–2005	HIV+ (35)	all*	HIV+ 133	HIV+ 57**	cytology [†] (12 months)	normal	SIL	HIV+ 47	HIV+ 7.4 [‡]	HIV+ 35%
Soncini et al. 2007 ²² Italy University Hospital 1993–2003	NS	mixed ^{††}	HIV+ 101	HIV+ (42)	cytology [†] , colposcopy(12 months)	normal	LSIL	HIV+ 7	HIV+ 2.0 [‡]	HIV+ 7%
Lehtovirta et al. 2006 ¹⁹ Finland University gynecological clinic 1989–2003	HIV+ (31)//	mixed ^{††}	HIV+ 55	HIV+ (53)//	cytology (6 months)	normal	HSIL	HIV+ 31	HIV+ 8.8 [‡]	HIV+ 30%
Hawes et al. 2006 ²⁷ Senegal STD clinics, sex workers, oversampling HR-HPV/HIV – 1994–1998	HIV+ (32) HIV- (31)	none	HIV+ 246 HIV- 381	HIV+/- (26) [§]	cytology (4 months)	normal	SIL	HIV+ 36 ^{**} HIV- 35 ^{**}	HIV+ 6.4 ^{**} HIV- 4.2 ^{**}	HIV+ 15% HIV- 9%

Author/year Country Study Population	Median (mean) age, years	ART use	Women with follow-up data (N)	Median (mean) follow- up time, months	Assessment method (intervals)	Baseline	Outcome	Cases (N)	Cases / 100 woman-years	Study cumulative risk
Schuman et al. 2003 ²⁶ USA HIV Epidemiology Research Study (HERS) 1993–1999	HIV+ 35 HIV- 34	mixed ^{††}	HIV+ 774 HIV- 391	HIV+ 48 HIV- 48	cytology [†] (6 months)	normal	HSIL	HIV+ 47 HIV- 4	HIV+ 1.6 HIV- 0.3	HIV+ 7% HIV- 1%
Branca et al. 2003 ³⁰ Italy DIANAIDS project, clinics 1997–1999	HIV+ (34) // HIV- (33) //	all [*]	HIV+ 73 HIV- 44	HIV+ (11) // HIV- (20) //	cytology (NS)	normal	HSIL	HIV+ 4 HIV- 1	HIV+ 6.2 [‡] HIV- 1.4 [‡]	HIV+ 5% HIV- 2%
Ellerbrock et al. 2000 ²⁴ USA New York Cervical Disease Study, STD clinics and drug treatment centers 1991–1996	HIV+ 35 HIV- 34	mixed ^{††}	HIV+ 328 HIV- 325	HIV+ (30) HIV- (33)	cytology, colposcopy, histology confirmation (6 months)	normal	LSIL	HIV+ 61 HIV- 12	HIV+ 7.6 HIV- 1.3	HIV+ 19% HIV- 4%
Delmas et al. 2000 ⁷ 12 European Countries European Study Group on Natural History of HIV Infection in Women; gynecology, STD, and drug treatment centers 1993–1998	HIV+ 31 //	mixed ^{††}	HIV+ 229	HIV+ 24	cytology [†] (6 months)	normal	HSIL	HIV+ 6 HIV- 4	HIV+ 0.7 HIV- 0.4	HIV+ 2% HIV- 1%
Petry et al. 1999 ²⁰ Germany university immunology center 1990–1998	HIV+ (33)	NS	HIV+ 88	HIV+ (21) [†]	cytology, colposcopy, histology confirmation (NS)	normal	SIL	HIV+ 67 HIV- 16	HIV+ 8.3 HIV- 1.8	HIV+ 20% HIV- 5%
Six et al. 1998 ¹⁰ France and French Guiana medical centers and STD clinics 1993–1995	HIV+ 3 // HIV- 29 //	mixed ^{††}	HIV+ 160 HIV- 118	HIV+/- 13 [§] //	cytology [†] (6 months)	normal	ASCUS and SIL	HIV+ 33 HIV- 6	HIV+ 19.0 [‡] HIV- 4.7 [‡]	HIV+ 21% HIV- 5%
Heard et al. 1995 ¹⁸ France HIV gyn. clinic 1991–1993	NS	mixed ^{††}	HIV+ 27	HIV+ 18	cytology and colposcopy (6 months)	normal	SIL	HIV+ 2	HIV+ 4.9 [‡]	HIV+ 7%

ART=antiretroviral therapy, HAART=highly active antiretroviral therapy, HIV=human immunodeficiency virus, SIL=squamous intraepithelial lesion, LSIL = low grade SIL, HSIL = high grade SIL, ASCUS=atypical cells of unknown significance, CIN=cervical intraepithelial neoplasia, STD=sexually transmitted disease, NS=not specified;

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* HAART;

[†] Some cases confirmed by histology;

[‡] Estimated from [(incident cases / (N normal at baseline * mean or median follow-up time)] * 100;

[§] HIV+ / - combined;

// For larger cohort;

[¶] Mixed ART/HAART, additional reference used²²;

** From personal communication with author;

^{††} Mixed ART/HAART;

^{†††} ART.

Table 2
Cervical neoplasia incidence estimates stratified by CD4 count in HIV-positive populations

Author/year Country	Median (mean) follow-up time, months*	Assessment method	Baseline	Outcome	ART use	CD4 count	Women with follow-up data (N)	Study cumulative risk	Risk Ratio(95% CI)
Sireta et al. 2007 ²¹ Germany	57 [†]	cytology [‡]	normal	SIL	all [§]	> 200	110	33%	0.4 (0.1, 1.0) ^{//}
						200	20	55%	REF
Lehtovirta et al. 2006 ¹⁹ Finland	(31)	cytology	normal	SIL	mixed [¶]	400	NS	NS	REF
						<400	NS	NS	1.6 (0.7, 3.7) ^{**}
Hawes et al. 2006 ²⁷ Senegal	(26)	cytology	normal	HSIL	none	> 500	102	6%	REF
						200–500	95	20%	1.6 (0.5, 4.9) ^{††}
						< 200	48	39%	1.7 (0.5, 5.6) ^{††}
Schuman et al. 2003 ²⁶ USA	35	cytology [‡]	normal	SIL	mixed [¶]	> 500	NS	NS	REF
						200–500	NS	NS	1.8 (1.1, 2.8)
						< 200	NS	NS	2.1 (1.3, 3.6)
Delmas et al. 2000 ⁷ 12 European Countries	24	cytology [‡]	normal	SIL	all [¶]	500	NS	NS	REF
						200–499	NS	NS	1.9 (1.0, 3.6) ^{##}
						< 200	NS	NS	2.9 (1.1, 8.0) ^{##}
						500	NS	NS	REF
						200–499	NS	NS	1.3 (0.6, 2.8) ^{##}
						< 200	NS	NS	1.7 (0.8, 3.5) ^{##}
						500	87	22%	REF
200–499	99	31%	1.6 (0.9, 2.8) ^{##}						
< 200	43	44%	1.9 (1.0, 3.7) ^{##}						
Six et al. 1998 ¹⁰ France and French Guiana	13	cytology [‡]	normal	ASCUS and SIL	none	> 500	46	17%	REF
						< 500	51	27%	1.6 ^{§§}

Author/year Country	Median (mean) follow-up time, * months	Assessment method	Baseline	Outcome	ART use	CD4 count	Women with follow- up data (N)	Study cumulative risk	Risk Ratio(95% CI)
Heard et al. 1995 ¹⁸ France	18	cytology and colposcopy	normal	SIL	mixed ^{///}	200 < 200	22 5	9% 0%	NS NS

ART=antiretroviral therapy, HAART=highly active antiretroviral therapy, SIL=squamous intraepithelial lesion, HSIL = high grade SIL, ASCUS=atypical cells of unknown significance, CI = confidence interval, NS=not stated

* For larger cohort;

[†] From personal communication with author;

[‡] Some cases confirmed by histology;

[§] HAART;

^{//} Odds ratio;

[¶] Mixed ART/HAART;

^{**} Adjusted for age;

^{††} Adjusted for age, employment as commercial sex worker, parity, birth in Senegal, and cytology reader;

^{‡‡} Adjusted for HPV detection;

^{§§} Estimated from the ratio of the study cumulative risks;

^{///} ART.

Table 3

Cervical neoplasia incidence estimates stratified by anti-retroviral use in HIV-positive populations

Author/year Country	Median (mean) follow-up time, months*	Assessment method	Baseline	Outcome	ART use	Women with follow-up data (N)	Risk Ratio(95% CI)
Minkoff et al. 2010 ³² USA	NS	cytology	normal	SIL	none HAART [†]	NS NS	REF 0.7 (0.3,1.9)
Sireira et al. 2008 ³¹ Germany	(35)	cytology [‡]	normal	SIL	none HAART	37 90	REF 1.8 (0.7, 4.7) §
Soncini et al., 2007 ²² Italy	NS	cytology [‡] colposcopy	normal	SIL	none HAART	31 43	REF 0.3 (0.1, 0.7) //
Lehtovirta et al. 2006 ¹⁹ Finland	(31)	cytology	normal	SIL	None ART [¶]	NS NS	REF 0.8 (0.4, 1.8) **
Schuman et al. 2003 ²⁶ USA	35	cytology [‡]	normal	SIL	None Sub-HAART ^{††} HAART	NS NS NS	REF 1.6 (1.1, 2.1) 1.2 (0.5, 2.9)

SIL=squamous intraepithelial lesion, ART=antiretroviral therapy, HAART=highly active antiretroviral therapy,

CI = confidence interval, NS=not stated

* For larger cohort;

[†] Includes only women adherent to HAART;

[‡] Some cases confirmed by histology;

§ Odds ratio;

// Hazard ratio;

¶ Mixed ART/HAART;

** Adjusted for age;

^{††} non-HAART combination therapy or monotherapy.

Table 4

Progression rate estimates of cervical neoplasia from HIV-positive populations

Author/year Country Study Population	Median (mean) age, years	ART use	Women with progression follow-up data (N)	Median (mean) follow-up time for progression, months	Assessment method (intervals)	Baseline	Outcome	Progressed (N)	Progression cases / 100 woman- years	Study cumulative risk
Omar et al. 2011 ²⁸ South Africa HIV wellness clinic 2003–2009	HIV+ 32* HIV- 31*	mixed [†]	HIV+ 242	HIV+ 31* HIV- 31*	cytology (6–12 months)	LSIL	HSIL	HIV+52	HIV+ 9.8	HIV+ 22%
Duerr et al. 2006 ³³ USA HIV Epidemiology Research Study (HERS) 1993– 1999	HIV+ 35 [‡] HIV- 34 [‡]	mixed [§]	HIV+ 148 HIV- 48	HIV+ 53* HIV- 53*	cytology (6 months)	ASCUS	SIL	HIV+ 89 HIV- 12	HIV+13.7// HIV- 5.7//	HIV+ 60% HIV- 25%
Nappi et al. 2005 ³⁷ Italy University clinic 1990–1997	HIV+ (27)* HIV- (28)*	NS	HIV+ 28 HIV- 30	NS	cytology confirmed by histology (3–6 months)	LSIL	HSIL	HIV+ 15 HIV- 7	NS	HIV+ 54% HIV- 23%
Del Mistro et al. 2004 ³⁸ Italy Infectious disease units of city hospitals 1994– 2002	HIV+ 33* HIV- 33*	mixed [§]	HIV+ 88	NS	cytology [¶] (6–12 months)	LSIL	HSIL	HIV+ 6	NS	HIV+ 7%
Kirby et al. 2004 ³⁴ USA University clinic 1996–NS	HIV+ 37* HIV- 37*	mixed**	HIV+ 64	HIV+ 29	cytology (6 months)	ASCUS	HSIL	HIV+ 5	HIV+ 3.2//	HIV+ 8%
Maassad et al. 2004 ³⁵ USA Women's Interagency HIV Study (WIHS)	HIV+ (38) HIV- (31)	mixed [§]	HIV+ 202 HIV- 21	HIV+/(40) ^{††}	cytology [¶] (6 months)	CIN I	CIN 2–3 or HSIL	HIV+ 8 HIV- 0	HIV+ 1.2 HIV- 0	HIV+ 4% HIV- 0%

Author/year Country Study Population	Median (mean) age, years	ART use	Women with progression follow-up data (N)	Median (mean) follow-up time for progression, months	Assessment method (intervals)	Baseline	Outcome	Progressed (N)	Progression cases / 100 woman- years	Study cumulative risk
university, public, and private medical centers and clinics 1994– 2002										
Robinson et al. 2002 ³⁶ USA 26 AIDS Clinical Trials Group sites, isoretinoin treatment study ^{††} 1996– 1999	NS	mixed [§]	HIV+ 52	HIV+ 11	cytology confirmed by histology (3–6 months)	CIN I	CIN2/3	HIV+ 13	HIV+ 26.2 ^{//}	HIV+ 25%
Calore et al. 2001 ⁴⁰ Brazil Infectology Institute 1996– 1999	HIV+ (35)	NS	HIV+ 31	NS	cytology (24–48 months)	LSIL	HSIL	HIV+ 2	NS	HIV+ 7%
Delmas et al. 2007 12 European Countries European Study Group on Natural History of HIV Infection in Women; gynecology, STD, and drug treatment centers 1993 – 1998	HIV+ 31 [*]	mixed [§]	HIV+ 115	HIV+ 18	cytology [¶] (6 months)	LSIL	HSIL	HIV+ 11	HIV+ 6.4 ^{//}	HIV+ 10%
La Ruche et al. 1999 ³⁹ Côte d'Ivoire Gynecology clinics 1995–1996	NS	NS	HIV+ 38 HIV– 56	NS	cytology (5 months)	LSIL	HSIL	NS	NS	HIV+ 18% HIV– 0%
Six et al. 1998 ¹⁰ France and French Guiana	HIV+ 31 [*] HIV– 29 [*]	mixed ^{**}	HIV+ 47 HIV– 7	HIV+/- 13 ^{**††}	cytology [¶] (6 months)	LSIL	HSIL	HIV+ 12 HIV– 0	HIV+ 23.6 ^{//} HIV– 0 ^{//}	HIV+ 26% HIV– 0%

Author/year Country Study Population	Median (mean) age, years	ART use	Women with progression follow-up data (N)	Median (mean) follow-up time for progression, months	Assessment method (intervals)	Baseline	Outcome	Progressed (N)	Progression cases / 100 woman- years	Study cumulative risk
medical centers and STD clinics 1993–1995										

ART=antiretroviral therapy, HAART=highly active antiretroviral therapy, HIV=human immunodeficiency virus, ASCUS=atypical cells of unknown significance, SIL=squamous intraepithelial lesion, LSIL = low grade SIL, HSIL = high grade SIL, CIN = cervical intraepithelial neoplasia, NS=not specified

* For larger cohort;

[†] HAART;

[‡] Additional reference used²⁶;

[§] Mixed ART/HAART;

^{||} Estimated from [(number progressed / (N at baseline * mean follow-up time)) * 100];

[¶] Some cases confirmed by histology;

** ART;

^{††} HIV+ / – combined;

^{†††} Control arm.

Table 5
Progression estimates for cervical lesions stratified by CD4 count in HIV-positive populations

Author/year Country	ART use	median (mean) follow-up time for progression, * months	Assessment method	Baseline	Outcome	CD4 count	Number of women with follow-up data	Study cumulative risk	Risk Ratio(95% CI)
Duerr et al. 2006 ³³ USA	mixed [‡]	53	cytology	ASCUS	SIL	>500	NS	NS	REF
						200-500	NS	NS	1.4 (0.7, 2.6)
						<200	NS	NS	1.7 (0.8, 3.6)
Nappi et al. 2005 ³⁷ Italy	NS	NS	cytology confirmed by histology	LSIL	HSIL	>200	15	33%	REF
						<200	13	77%	6.67 [‡] (1.2, 35.7)
Six et al. 1998 ¹⁰ France and French Guiana	mixed [§]	13	cytology//	LSIL	HSIL	>500	9	0%	NS
						200-500	18	31%	NS
						<200	20	41%	NS

ART=antiretroviral therapy, CI= confidence interval, HAART=highly active antiretroviral therapy, HIV=human immunodeficiency virus, LSIL = low grade SIL, HSIL = high grade SIL, NS=not specified

* For larger cohort;

[‡]Mixed ART/HAART;

[‡]Odds ratio, not risk ratio;

[§] ART;

// Some cases confirmed by histology.