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Cervical cancer risk in women living with HIV across four continents: a multicohort study

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Abstract

We compared invasive cervical cancer (ICC) incidence rates in Europe, South Africa, Latin and North America among women living with HIV who initiated antiretroviral therapy (ART) between 1996 and 2014. We analyzed cohort data from the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. We used flexible parametric survival models to determine regional ICC rates and risk factors for incident ICC. We included 64,231 women from 45 countries. During 320,141 person-years (pys), 356 incident ICC cases were diagnosed (Europe 164, South Africa 156, North America 19, Latin America 17). Raw ICC incidence rates per 100,000 pys were 447 in South Africa (95% confidence interval [CI] 382–523), 136 in Latin America (95% CI 85–219), 76 in North America (95% CI 48–119), and 66 in Europe (95% CI 57–77). Compared with European women ICC rates at 5 years after ART initiation were more than double in Latin America (adjusted hazard ratio [aHR] 2.43, 95% CI 1.27–4.68) and 11-times higher in South Africa (aHR 10.66, 95% CI 6.73–16.88), but similar in North America (aHR 0.79, 95% CI 0.37–1.71). Overall, ICC rates increased with age (>50 years versus 16–30 years, aHR 1.57, 95% CI 1.03–2.40) and lower CD4 cell counts at ART initiation (per 100 cell/μl decrease, aHR 1.25, 95% CI 1.15–1.36). Improving access to early ART initiation and effective cervical cancer screening in women living with HIV should be key parts of global efforts to reduce cancer-related health inequities.

Keywords

Cervical cancer; HIV; incidence rate; cohort study

Introduction

Vast global inequities in the burden of invasive cervical cancer (ICC) exist.[1,2] While access to effective screening and treatment of pre-cancerous cervical lesions has substantially reduced the risk of developing ICC in high-income countries, ICC remains a common cause of premature mortality and morbidity in women in low- and middle-income countries.[1,2] ICC disproportionally affects women living with human immunodeficiency virus (HIV), who are more likely to have persistent co-infection with high-risk human papillomavirus (HPV) types,[3] to develop pre-cancerous cervical lesions,[4] and to progress to ICC than HIV-negative women.[4] The advent and scale-up of combination antiretroviral therapy (ART) has led to a dramatic decline in morbidity and mortality from many HIV-associated diseases,[5] but these decreases have not occurred for ICC.[6,7] Indeed, as life expectancy after starting ART increases, there is more time for pre-cancerous cervical lesions to develop into ICC, but early initiation of ART seems to lower HPV co-infection rates and improve control of pre-cancerous cervical lesions.[8]

Global inequities in ICC incidence rates among women living with HIV have not been assessed previously. Our aim was to assess such inequities by comparing ICC incidence rates across different geographic regions among women who had initiated ART. Additionally, we examined risk factors for developing ICC in these women.

Methods

Databases

We analyzed routinely collected clinical, demographic, laboratory, and treatment data of women enrolled in observational HIV cohorts that participate in the International epidemiology Databases to Evaluate AIDS (IeDEA) or the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. IeDEA has regional data centers in the Asia-Pacific, Australia, North America, Latin America and four African regions. Cohorts from the following IeDEA regions initially contributed data to this study: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD),[9] the Caribbean, Central and South America network for HIV epidemiology (CCASAnet),[10] IeDEA Southern Africa,[11] and IeDEA Asia-Pacific.[12] For the IeDEA Southern Africa region, we restricted the analysis to two cohorts from South Africa that reduced under-reporting of cancer cases in the HIV cohorts through record linkages with the National Cancer Registry.[13] COHERE is a collaboration of observational HIV cohorts across Europe.[14] It contributed data from 24 cohorts, covering 36 countries. All cohorts obtained ethical approval from local ethics committees or institutional review boards, and the Cantonal Ethics Committee of Bern (number 028/2015) also granted ethical approval for this study.

Inclusion criteria and definitions

We restricted the analysis to cohorts that systematically collected cancer data or had enhanced their data through record linkages with cancer registries. We included women living with HIV who started ART after 1995 at 16 years or older. We excluded women who started ART before enrolment into cohort, women without follow-up after ART initiation, and women without any CD4 cell count measurements at ART initiation or during follow-up. We also excluded cohorts with less than 100 eligible women and the Asia-Pacific region because of small sample size (post-hoc decision). We analyzed ICC cases diagnosed any time after ART initiation as incident cases and excluded women diagnosed with ICC before or at ART initiation (prevalent ICC cases) from the analysis. We defined ART as a combination of at least three antiretroviral drugs from any class, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors (NNRTIs). We assumed that women remained on ART and did not consider treatment interruptions and terminations. CD4 cell count at ART initiation was defined as the cell count closest to ART initiation, during the period within 180 days before to seven days after initiation.

Statistical analyses

We calculated raw ICC incidence rates by dividing the number of incident ICC cases by person-years (pys) at risk. Time at risk was measured from ART initiation to ICC diagnosis, last follow-up visit, death, or database closure, whichever happened first. We used proportional hazard flexible parametric survival models[15] to estimate regional ICC incidence rates and to identify risk factors for developing ICC. We compared ICC rates at 2 years and 5 years after ART initiation across geographic regions. We used restricted cubic splines with 4 degrees of freedom and allowed for time-dependent region-effects with 2 degrees of freedom to model the baseline hazard. We performed likelihood ratio tests to test interactions between risk factors and regions. We assessed the following potential risk factors in the analysis: age at ART initiation (16–30, 31–50, >50 years); first-line ART regimen (NNRTI-based, PI-based, other); calendar period of ART initiation (1996–1998, 1999–2003, 2004–2007, 2008–2014); CD4 cell count at ART initiation; and current (time-updated) CD4 cell count. We treated CD4 cell count at ART initiation and current CD4 cell count as continuous variables. Analyses including CD4 cell count at ART initiation were restricted to women with available data on this variable. HIV RNA load at ART initiation was assessed in descriptive analyses.

We fit a crude model that included only the time-dependent region-effects, resulting in region-specific baseline hazards, and no other risk factors. The main adjusted model included region, CD4 cell count at ART initiation, age at ART initiation, first-line ART regimen, and calendar period of ART initiation. From the main adjusted model, we predicted ICC incidence rates for women with a specific set of risk factors, i.e. for women who initiated an NNRTI-based regimen between 2008–2014 at age 31–50 years with a CD4 cell count of 200 cells/μl. In a sensitivity analysis, the adjusted model included current (time-updated) CD4 cell count instead of CD4 cell count at ART initiation. In a second sensitivity analysis, we excluded ICC cases diagnosed within the first three months after ART initiation as prevalent cases and women with less than three months of follow-up. Results are

presented as medians with interquartile ranges (IQR), number and percentages of women, incidence rates per 100,000 pys and hazard ratios (HRs) with 95% confidence intervals (CIs). We used Stata 14 (Stata Corporation, College Station, Texas, USA) and R (R Foundation, Vienna, Austria) for our analyses.

Results

Descriptive analyses

The merged dataset included information on 126,063 women living with HIV. We excluded 44,419 women because they did not receive ART and another 14,413 women for reasons detailed in Supplementary Figures S1-S5. We made a post-hoc decision to exclude the Asia-Pacific region because too few eligible women remained after applying our exclusion criteria.

We included data on 64,231 women living with HIV, drawn from 36 cohorts and 45 countries across Europe, North America, Latin America, and South Africa (Figure 1). Overall, median age at ART initiation was 34.9 years (IQR 29.3–41.9), and was higher in North America (38.6 years) than in other regions (Table 1). Median CD4 cell count at ART initiation was 115 cells/μl (IQR 50–182) in South Africa, 178 cells/μl (IQR 74–281) in Latin America, and 241 cells/μl in both North America and Europe (Table 1). In South Africa, less than 1% of women started ART before 2004, but 26% of women in Latin America, 40% in Europe and 70% in North America initiated ART between 1996 and 2003. Most women in South Africa (93%) and Latin America (70%) received an NNRTI-based first-line regimen, but the majority of women in the European (55%) and North American (60%) cohorts received a PI-based first-line regimen. Median follow-up after ART initiation was around 5 years in Europe, North, and Latin America, but shorter in South Africa (2.1 years).

Over 320,141 pys of follow-up, 356 incident ICC cases were diagnosed (164 in Europe, 156 in South Africa, 19 in North America, and 17 in Latin America). In women who developed ICC, median time from ART initiation to ICC diagnosis was 1.9 years (IQR 0.7–4.2), and it ranged from 1.7 years in South Africa and North America to 2.6 years in Latin America (Supplementary Table S1). Median age at ICC diagnosis was 33 years in Latin America, and 38–40 years in South Africa, North America, and Europe. Median CD4 cell count at ICC diagnosis ranged from 275 cells/μl in Latin America to 370 cells/μl in North America.

Comparing ICC risk across regions

The raw ICC incidence rate was highest in South Africa, with 447/100,000 pys (95% CI 382–523), followed by Latin America (136/100,000 pys; 95% CI 85–219), North America (76/100,000 pys; 95% CI 48–119), and Europe (66/100,000 pys; 95% CI 57–77). In Europe, North America, and Latin America, there was some evidence for a decrease in crude and adjusted ICC incidence rates after more than one year on ART, except in South Africa (Figure 2). In crude analyses, ICC rates at 5 years after ART initiation were 11-times higher in women living with HIV in South Africa than in their European counterparts (HR 11.06, 95% CI 7.80–15.68). The much higher ICC rate in South African women was not explained by differences in CD4 cell count at ART initiation, age at ART initiation, first-line ART

regimen, or calendar period of ART initiation (adjusted HR [aHR] 10.66, 95% CI 6.73–16.88; see Table 2). In crude (HR 2.32, 95% CI 1.24–4.31) and adjusted analyses (aHR 2.43, 95% CI 1.27–4.68), ICC rates at 5 years after ART initiation were more than twice as high in Latin American as in European women. In North American and European women, ICC rates after ART initiation were comparable in crude (HR 0.98, 95% CI 0.48–1.99) and adjusted analyses (aHR 0.79, 95% CI 0.37–1.71). The regional comparisons of ICC rates were similar at 2 years after ART initiation (Table 2). Also at 2 years after ART initiation, ICC rates were much higher in South Africa than in Europe (aHR 6.23, 95% CI 4.29–9.05). When we excluded ICC cases diagnosed within the first three months after ART initiation in a sensitivity analysis, results did not meaningfully change (Supplementary Table S2).

Risk factors for incident ICC

We did not find evidence of regional variation in the effect of CD4 cell count at ART initiation, age at ART initiation, first-line ART regimen, or calendar period of ART initiation on the risk of developing ICC (all p-values for interaction ≥ 0.13, see Table 3). Across all regions combined, the risk of developing ICC increased among women who initiated ART at lower CD4 cell counts (per 100 cell/μl decrease, aHR 1.25, 95% CI 1.15–1.36), and with older age at ART initiation (>50 years versus 16–30 years, aHR 1.57, 95% CI 1.03–2.40). There was no association between type of first-line ART regimen and the risk of developing incident ICC (PI-based versus NNRTI-based, aHR 1.05, 95% CI 0.79–1.41), and we did not observe a relevant decline in ICC rates by calendar period of ART initiation. The effects of the risk factors assessed in the main adjusted model remained similar when we excluded ICC cases diagnosed within the first three months after ART initiation from the analysis (Supplementary Table S3).

In a sensitivity analysis, we assessed the effect of current CD4 cell count on the risk of developing ICC and found that it varied across regions (p-value for interaction = 0.017). In analyses adjusted for age, first-line ART regimen, and calendar period of ART initiation, we did not find an association between current CD4 cell count and risk of developing ICC in South Africa (per 100 cells/μl decrease, aHR 1.00, 95% CI 0.92–1.10) or North America (aHR 1.08, 95% CI 0.90–1.30). However, a decrease of 100 cells/μl in current CD4 cell count increased the risk of developing ICC by 18% in European women (aHR 1.18, 95% CI 1.10–1.27) and 41% in Latin American women (aHR 1.41, 95% CI 1.07–1.86; see Supplementary Table S4 and Supplementary Figure S6).

Discussion

Across geographic regions, we found large inequities for cervical cancer incidence in women living with HIV. ICC incidence rates were high in women living with HIV in all regions studied, but the risk of developing ICC was much higher in women who had initiated ART in South Africa or Latin America than in women who had initiated ART in Europe or North America. Across all regions combined, the risk of developing ICC increased with older age and lower CD4 cell counts at ART initiation.

We believe this is the first study to provide a comparison of ICC incidence rates among women living with HIV across several geographic regions. To improve comparability of

results across regions, we applied the same inclusion criteria and statistical methods across the whole dataset. With more than 60,000 women and 356 ICC cases included, this is also the largest study of ICC incidence in women living with HIV. However, several limitations of our study need to be acknowledged. Less than 20 ICC cases each were recorded in Latin America and North America. Thus, our comparison of ICC rates between those regions and Europe are of limited precision. ICC case identification and validation are likely to vary across regions and may have affected observed regional differences in ICC rates. Our results for South Africa may not be generalizable to Southern Africa as a region, given that we restricted our analyses to two urban cohorts in South Africa, which had been linked with the National Cancer Registry to reduce under-reporting of ICC cases. Because we included all women who started ART, irrespective of whether they remained in treatment, our results may not be representative of women who stayed continuously on ART. HIV RNA measurements at ART initiation were missing for one-third of women included in Latin America, and almost 80% of women from South Africa. Therefore, we could not use HIV RNA load to evaluate treatment response over time. Information on duration of HIV infection, HPV co-infection status, cervical cancer screening history, and smoking status was generally not available. Thus, we could not explore their effects on the risk of being diagnosed with ICC or adjust the regional comparisons for these potential confounders. Furthermore, as data on history of hysterectomy were not available, we could not exclude women who were no longer at risk of developing ICC. It would also have been interesting to assess ICC-related inequities in more depth, but we did not have data on ICC stage at diagnosis, for example.

We found that across all regions women living with HIV were at high risk of developing ICC after ART initiation. Most previous studies did not restrict their analyses to women who had initiated ART, but rather report ICC incidence estimates for women living with HIV irrespective of ART use.[6,16–18] The raw ICC incidence rates in women living with HIV who had initiated ART, ranging from 66/100,000 pys in Europe to 447/100,000 pys in South Africa, were substantially higher than the ICC incidence rates reported for women from the general population in the included regions (≤30/100,000 pys).[2] In our study, ICC rates after ART initiation were by far highest in South Africa, followed by Latin America, and they were lower in women who had started ART in North America or Europe. These findings corroborate the regional ICC incidence rate pattern in the general population,[2] but the difference between South Africa and other regions is even more pronounced among women living with HIV.

The high ICC incidence rates we found in women from South Africa are similar to ICC incidence rates in women living with HIV in the United States in the early 1990s.[7] In the United States, ICC incidence rates in women living with HIV had already dropped in the mid-1990s, before ART became available, and this drop has partly been attributed to better screening and more effective treatment of pre-cancerous cervical lesions.[7] The extent to which ART protects women living with HIV from developing ICC is still being explored. Although ART reduces the prevalence of high-risk HPV in women living with HIV and promotes regression of cervical lesions,[8] many women in our analyses, notably in South Africa, may have started ART too late, when potentially irreversible pre-cancerous cervical lesions were already present. Furthermore, not all women in our study would have achieved

sustained suppression of HIV RNA, and high HIV RNA loads have been associated with an increased risk of HPV infection and cervical pre-cancerous lesions.[19] Low CD4 cell counts have also been associated with a higher risk of HPV infection[3] and development of severe cervical lesions.[20] Accordingly, several studies showed an increased ICC risk in women with low nadir,[21] baseline,[18] or current CD4 cell counts.[17] It remains a matter of debate at what stage of cervical carcinogenesis the effect of HIV-related immunodeficiency is largest. Across all regions combined, we found that the risk of developing ICC increased in women who initiated ART at low CD4 cell counts. High current CD4 cell counts had a protective effect in Latin America and Europe, but not in North America and South Africa.

Our analyses revealed massive regional differences in ICC rates in women living with HIV. Several factors could account for this finding. HPV prevalence in women living with HIV in sub-Saharan Africa or Latin America is higher than in North America or Europe,[22] and this may contribute to the increased ICC burden in South African and Latin American women living with HIV. Women in South Africa and Latin America also tended to initiate ART at lower CD4 cell counts than women in Europe, and low CD4 cell counts at ART initiation increased the risk of developing ICC. Nevertheless, in our analyses large regional differences in ICC rates persisted after adjusting for CD4 cell counts. Therefore, inequities in access to effective cervical cancer screening and treatment of pre-cancerous cervical lesions are likely to be the main driver of regional variation in ICC rates in women living with HIV. Substantial global efforts are needed to improve cervical cancer screening and treatment for women living with HIV, and to promote national HPV vaccination programmes. Unfortunately, most Southern African countries and some regions of Latin America lack the resources to treat ICC.[23,24]

The availability of HPV vaccination and the long natural history from HPV infection through cervical intraepithelial neoplasia to invasive cancer make ICC particularly amenable to primary and secondary prevention.[25] However, it has been estimated that in 2014 less than one-third of female adolescents aged 10–20 years in high-income countries and only 1% in low-income countries had received the full course of HPV vaccine.[26] At present, data on HPV vaccination coverage among women living with HIV are lacking.[27] Access to screening services with early detection and treatment of pre-cancerous cervical lesions remains key for ICC prevention in women living with HIV. However, there are extensive regional differences in access to effective cervical cancer screening. Less than 10% of women living in low-income countries have access to effective cervical cancer screening as compared to more than 60% in high-income countries.[28] Integrating cervical cancer screening services into established HIV care programmes may facilitate screening access for women living with HIV and improve sustainability of screening programmes.[29] Yet, it remains unclear how many women living with HIV actually receive regular screening for pre-cancerous cervical lesions. HIV cohorts and integrated cervical cancer screening services often do not systematically collect patient-level data on screening and treatment of pre-cancerous cervical lesions.[30] Rigorous patient-level monitoring of cervical cancer screening and treatment programmes is essential to identify coverage gaps and target interventions.[30]

Conclusion

Our finding that women living with HIV who initiated ART in South Africa or Latin America were at much higher risk of developing ICC than women in North America or Europe reveals drastic global health inequities. ICC prevention through early ART initiation and scale up of effective cervical cancer screening services for women living with HIV, alongside the promotion of global access to HPV vaccination should be key parts of international efforts to reduce cancer-related health inequities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

FB received fees from ViiV Healthcare, Janssen, BMS, Gilead, and MSD for educational presentations and research grants from Gilead and Janssen. MJG has served as ad hoc member on Advisory HIV Boards to Merck, ViiV and

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Abbreviations:

aHR	adjusted hazard ratio
ART	antiretroviral therapy
CI	confidence interval
COHERE	Collaboration of Observational HIV Epidemiological Research in Europe
HIV	human immunodeficiency virus
HPV	human papillomavirus
ICC	invasive cervical cancer
IeDEA	International epidemiology Databases to Evaluate AIDS
IQR	interquartile range
pys	person-years
NNRTI	non-nucleoside reverse transcriptase inhibitor
PI	protease inhibitor

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Novelty and impact:

Our study compares invasive cervical cancer (ICC) rates among women living with HIV who initiated antiretroviral therapy (ART) across different geographic regions. It shows that ICC incidence rates are particularly high in women living with HIV in South Africa or Latin America. ICC prevention through early ART initiation, equitable access to effective cervical cancer screening, and promotion of human papillomavirus vaccination should be key elements of global efforts to reduce cancer-related health inequities.

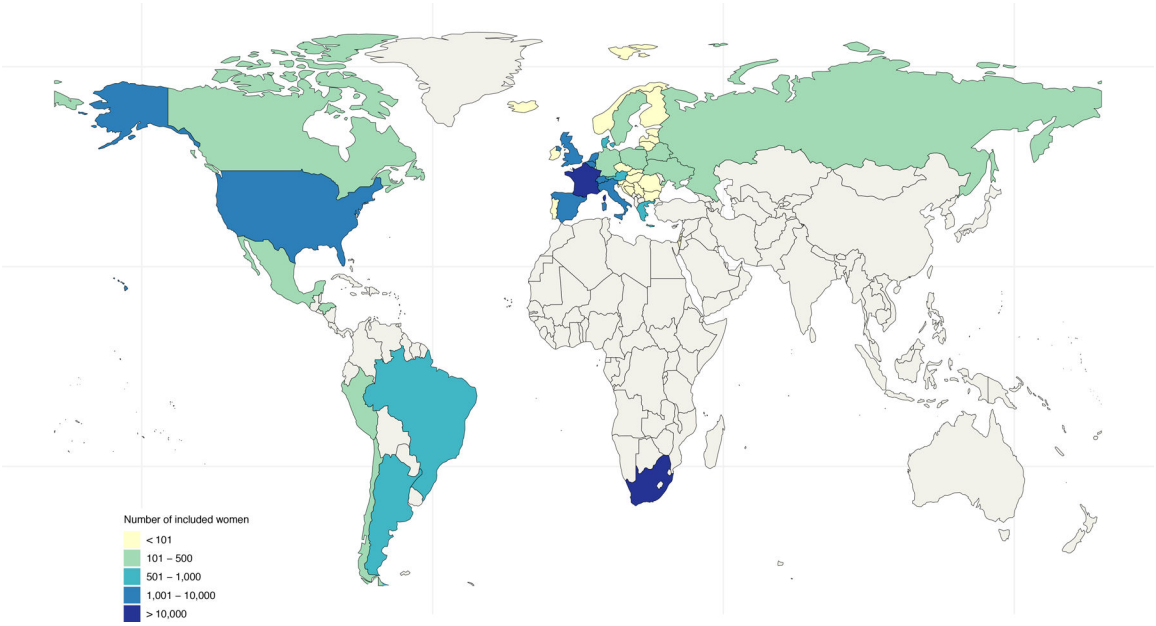

Figure 1.
Map of countries that contributed cohort data; number of included women, by country.

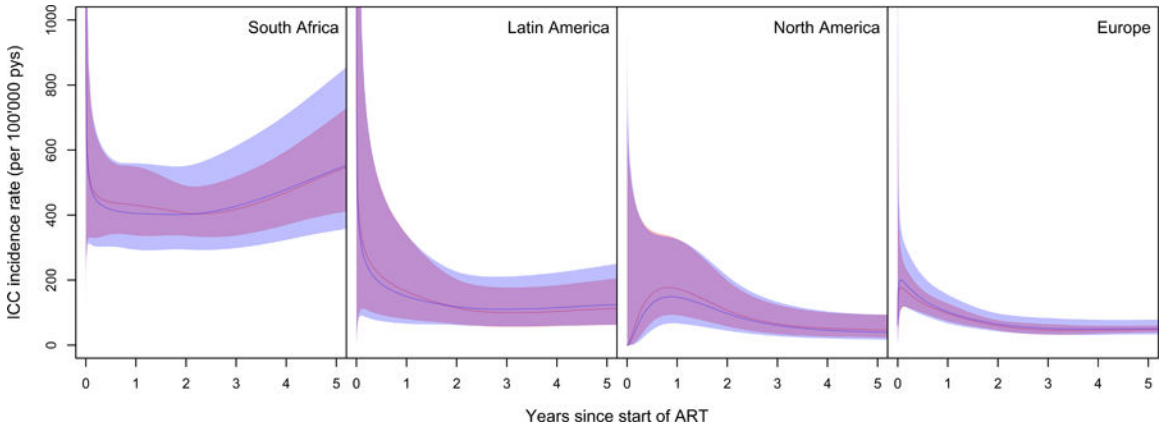

Figure 2.

Regional ICC incidence rates with 95% confidence intervals by time since ART initiation, predicted from the crude model (red) and the main adjusted model (blue) for women who initiated an NNRTI-based regimen between 2008–2014, at age 31–50 years, with a CD4 cell count of 200 cells/μl.

Table 1:

Characteristics of included women at ART initiation.

	South Africa N (%)	Latin America N (%)	North America N (%)	Europe N (%)
All women	13,569 (100%)	2,261 (100%)	4,120 (100%)	44,281 (100%)
Median follow-up time (IQR) [years]	2.1 (0.8–4.1)	5.0 (2.1–8.5)	5.4 (2.3–9.9)	4.8 (2.0–8.5)
Median age at ART initiation (IQR) [years]	35.1 (29.7–41.7)	35.4 (29.3–43.6)	38.6 (32.4–44.8)	34.6 (29.0–41.5)
Age at ART initiation [years]				
16–30	3,584 (26%)	627 (28%)	693 (17%)	12,934 (29%)
31–50	8,969 (66%)	1,363 (60%)	2,947 (72%)	26,944 (61%)
>50	1,016 (7%)	271 (12%)	480 (12%)	4,403 (10%)
First-line ART regimen				
NNRTI-based	12,594 (93%)	1,579 (70%)	1,261 (31%)	16,724 (38%)
PI-based	939 (7%)	623 (28%)	2,476 (60%)	24,325 (55%)
Other ART	36 (<1%)	59 (3%)	383 (9%)	3,232 (7%)
Year of ART initiation				
1996–1998	0 (0%)	26 (1%)	1,600 (39%)	4,260 (10%)
1999–2003	51 (<1%)	560 (25%)	1,276 (31%)	13,236 (30%)
2004–2007	6,791 (50%)	801 (35%)	864 (21%)	12,821 (29%)
2008–2014	6,727 (50%)	874 (39%)	380 (9%)	13,964 (32%)
Median CD4 cell count at ART initiation (IQR) [cells/μl]	115 (50–182)	178 (74–281)	241 (107–385)	241 (129–363)
CD4 cell count at ART initiation [cells/μl]				
< 50	3,113 (23%)	340 (15%)	577 (14%)	4,676 (11%)
50–99	2,402 (18%)	274 (12%)	303 (7%)	3,271 (7%)
100–199	4,733 (35%)	465 (21%)	663 (16%)	7,890 (18%)
200–349	1,821 (13%)	601 (27%)	1,047 (25%)	13,122 (30%)
350–499	276 (2%)	154 (7%)	587 (14%)	6,146 (14%)
500–699	139 (1%)	74 (3%)	349 (8%)	3,069 (7%)
≥ 700	66 (<1%)	30 (1%)	170 (4%)	1,638 (4%)
Missing	1,019 (8%)	323 (14%)	424 (10%)	4,469 (10%)
Median HIV RNA at ART initiation (IQR) [log10 copies/ml]	4.4 (2.6–5.2)	4.8 (4.0–5.3)	4.3 (3.4–5.0)	4.5 (3.7–5.1)
HIV RNA at ART initiation [log10 copies/ml]				
< 2.7	788 (6%)	91 (4%)	608 (15%)	4,704 (11%)
2.7–3.9	404 (3%)	260 (11%)	806 (20%)	7,319 (17%)
4.0–4.9	870 (6%)	585 (26%)	1,218 (30%)	14,051 (32%)
≥ 5.0	984 (7%)	568 (25%)	946 (23%)	11,764 (27%)
Missing	10,523 (78%)	757 (33%)	542 (13%)	6,443 (15%)

ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease-inhibitor; RNA, ribonucleic acid.

Table 2:
Comparison of ICC rates between different regions and Europe:

Crude and adjusted HRs for ICC at 2 years and 5 years after ART initiation in women living with HIV.

	At 2 years		At 5 years	
	Crude HR (95% CI)	**Adjusted HR* (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
Region				
Europe	1.00	1.00	1.00	1.00
North America	1.81 (0.94 – 3.48)	1.51 (0.73 – 3.12)	0.98 (0.48 – 1.99)	0.79 (0.37 – 1.71)
Latin America	1.93 (1.09 – 3.42)	1.83 (0.99 – 3.37)	2.32 (1.24 – 4.31)	2.43 (1.27 – 4.68)
South Africa	6.84 (5.20 – 9.00)	6.23 (4.29 – 9.05)	11.06 (7.80 – 15.68)	10.66 (6.73 – 16.88)

*Adjusted for CD4 cell count at ART initiation, age at ART initiation, first-line ART regimen, and calendar period of ART initiation.

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; ICC, invasive cervical cancer.

Table 3:

Adjusted hazard ratios for the effect of different factors on the risk of developing incident ICC in women who have initiated ART.

	Hazard ratio* (95% CI)	p-value for interaction**
CD4 cell count at ART initiation		0.76
per 100 cells/µl decrease	1.25 (1.15 – 1.36)	
Age at ART initiation [years]		0.34
16–30	1.00	
31–50	1.38 (1.05 – 1.81)	
>50	1.57 (1.03 – 2.40)	
First-line ART regimen		0.21
NNRTI-based	1.00	
PI-based	1.05 (0.79 – 1.41)	
Other ART	0.57 (0.27 – 1.18)	
Year of ART initiation		0.13
1996–1998	1.49 (0.92 – 2.42)	
1999–2003	1.19 (0.80 – 1.77)	
2004–2007	0.83 (0.61 – 1.14)	
2008–2014	1.00	

*Adjusted for region, CD4 cell count at ART initiation, age at ART initiation, calendar year of ART initiation, and first-line ART regimen.

**Derived from likelihood ratio test comparing the adjusted model with and without the interaction of a specific variable with region.

ART, antiretroviral therapy; CI, confidence interval; ICC, invasive cervical cancer; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease-inhibitor