

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

The AIDS-defining Cancer Project Working Group of IeDEA and COHERE in EuroCoord

### **Supplementary material**

#### **Figures**

- **Supplementary Figure S1:** Identification of study population for analysis. The flow diagram shows the number of included and excluded patients.
- **Supplementary Figure S2:** Identification of study population for the European region.
- **Supplementary Figure S3:** Identification of study population for the North American region.
- **Supplementary Figure S4:** Identification of study population for the Latin American region.
- **Supplementary Figure S5:** Identification of study population for the South African region.

**Supplementary Figure S6:** ICC incidence rates by time since ART initiation and current CD4 cell count (cells/ $\mu$ l) predicted from the second adjusted model (sensitivity analysis) for women living with HIV who initiated an NNRTI-based first-line ART regimen between 2008-2014 at age 31-50 years.

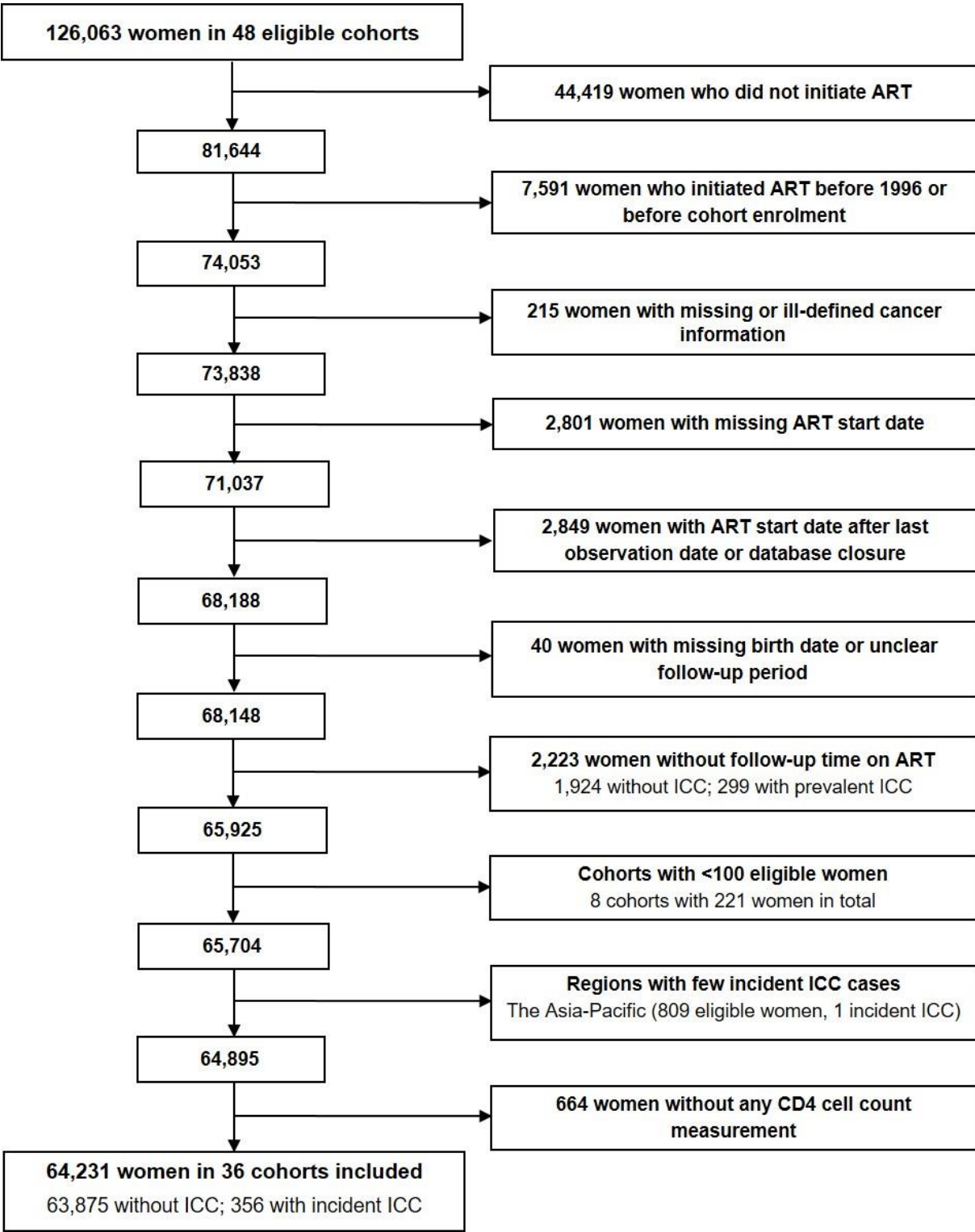
#### **Tables**

- **Supplementary Table S1:** Characteristics of women with incident ICC.
- **Supplementary Table S2:** 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; sensitivity analysis excluding ICC cases diagnosed within the first three months after ART initiation.
- **Supplementary Table S3:** Sensitivity analysis of regional risk factors for incident ICC in women who have initiated ART, excluding ICC cases diagnosed within the first three months after ART initiation.
- **Supplementary Table S4:** Sensitivity analysis of regional risk factors for incident ICC in women who have initiated ART, including current CD4 cell count instead of CD4 cell count at ART initiation.

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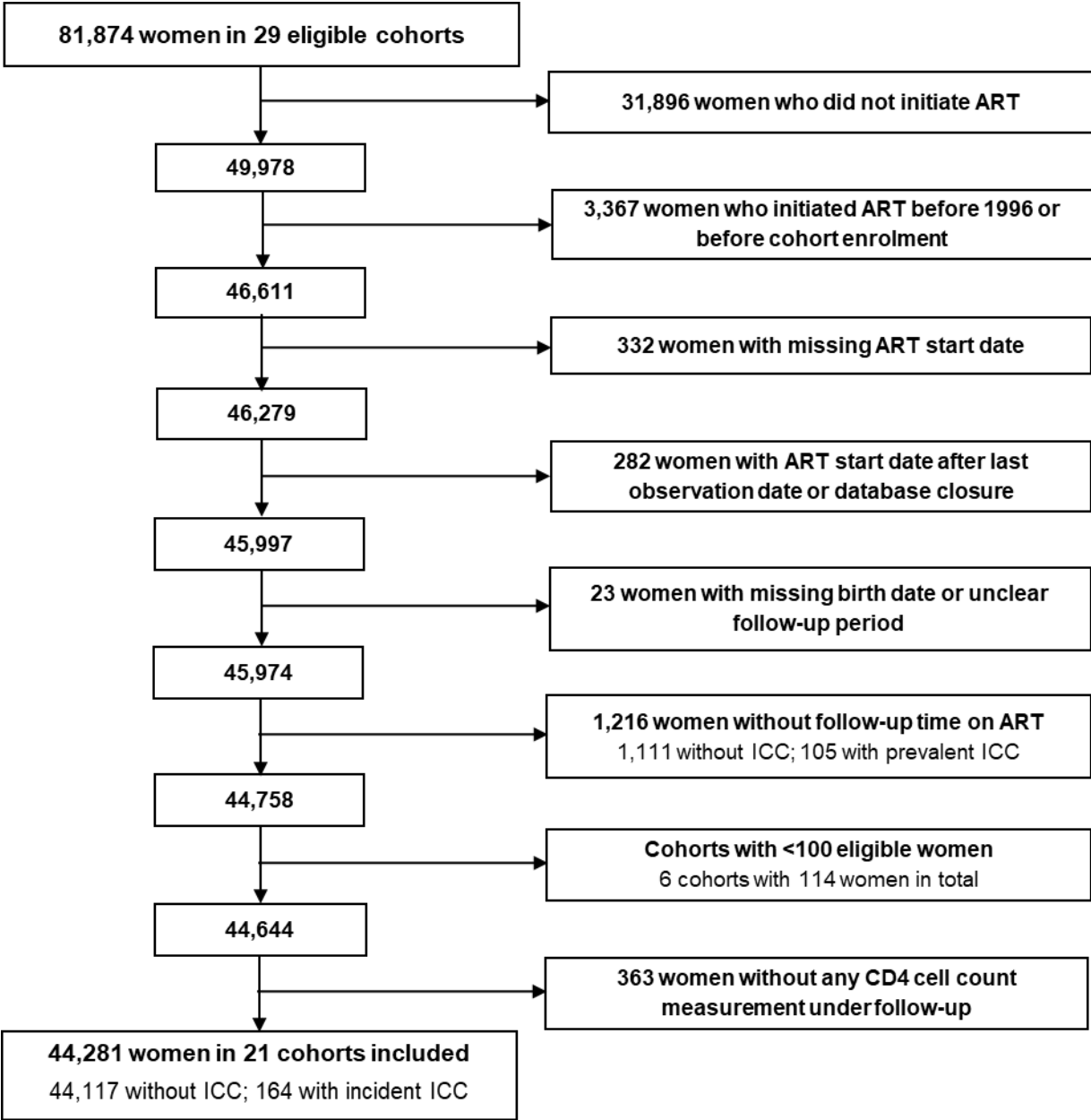
- **Detailed acknowledgements of consortia contributing data to this analysis.**

**Supplementary Figure S1:** Identification of study population for analysis. The flow diagram shows the number of included and excluded women.

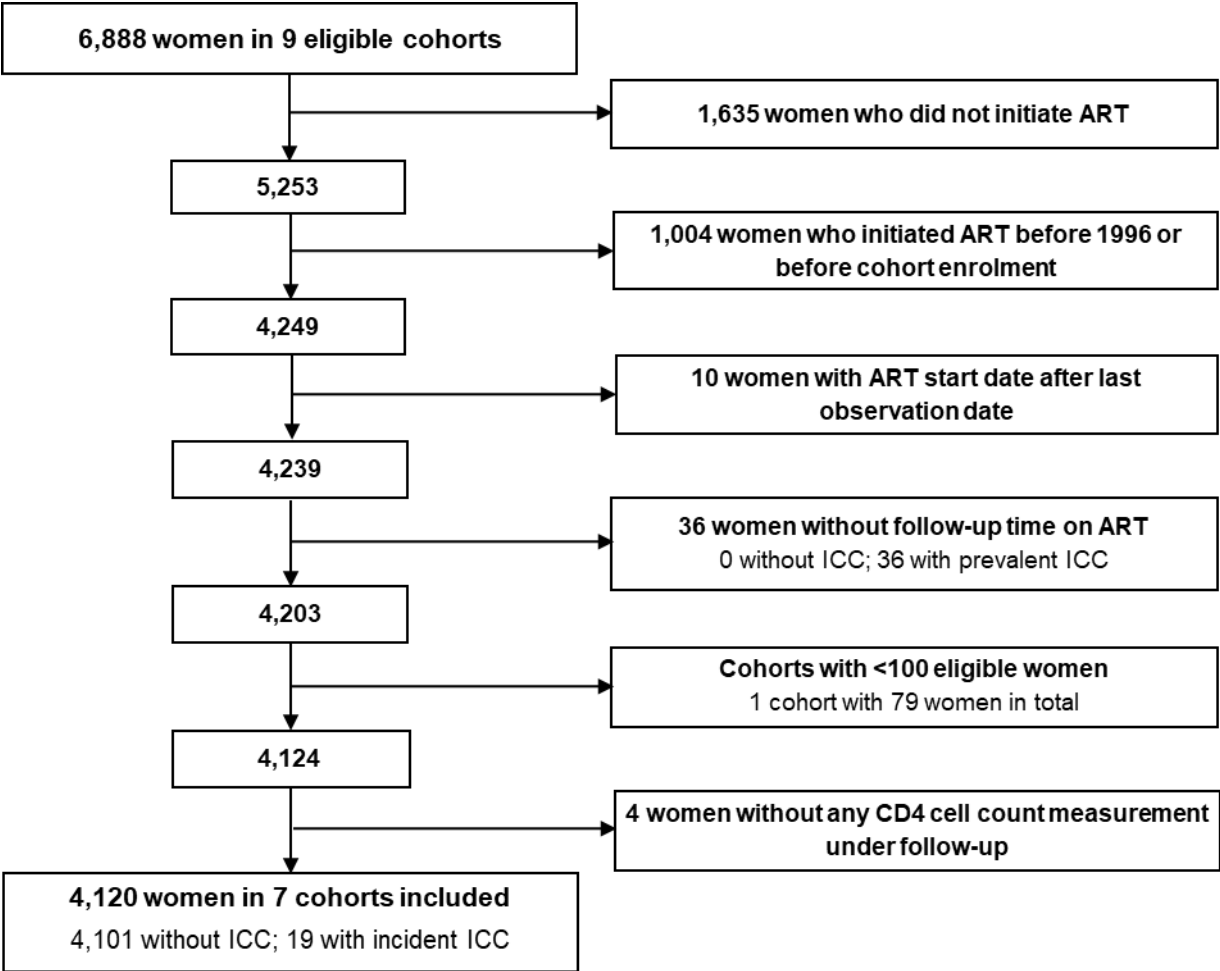


ART, antiretroviral therapy; ICC, invasive cervical cancer.

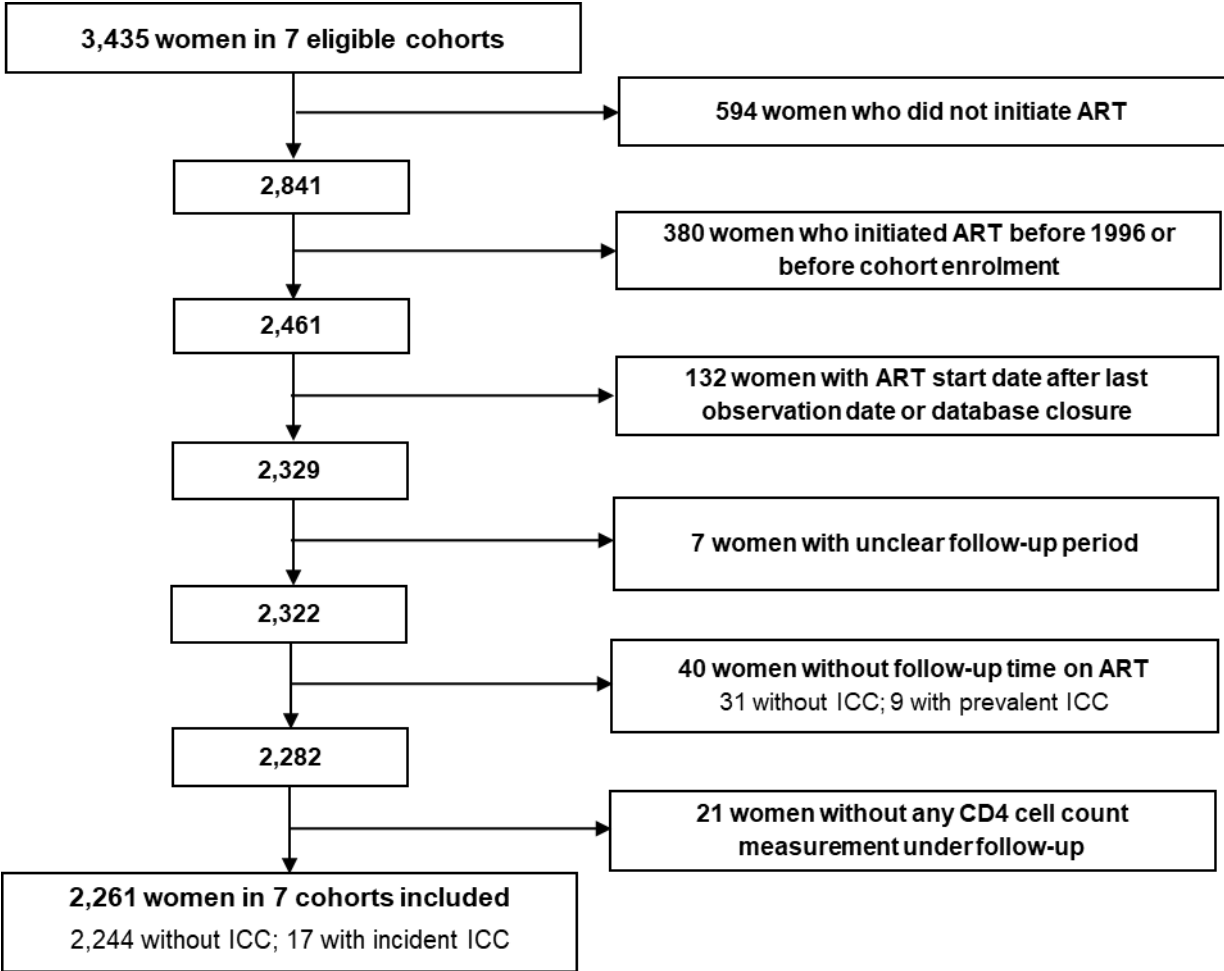
**Supplementary Figure S2:** Identification of study population for the European region.



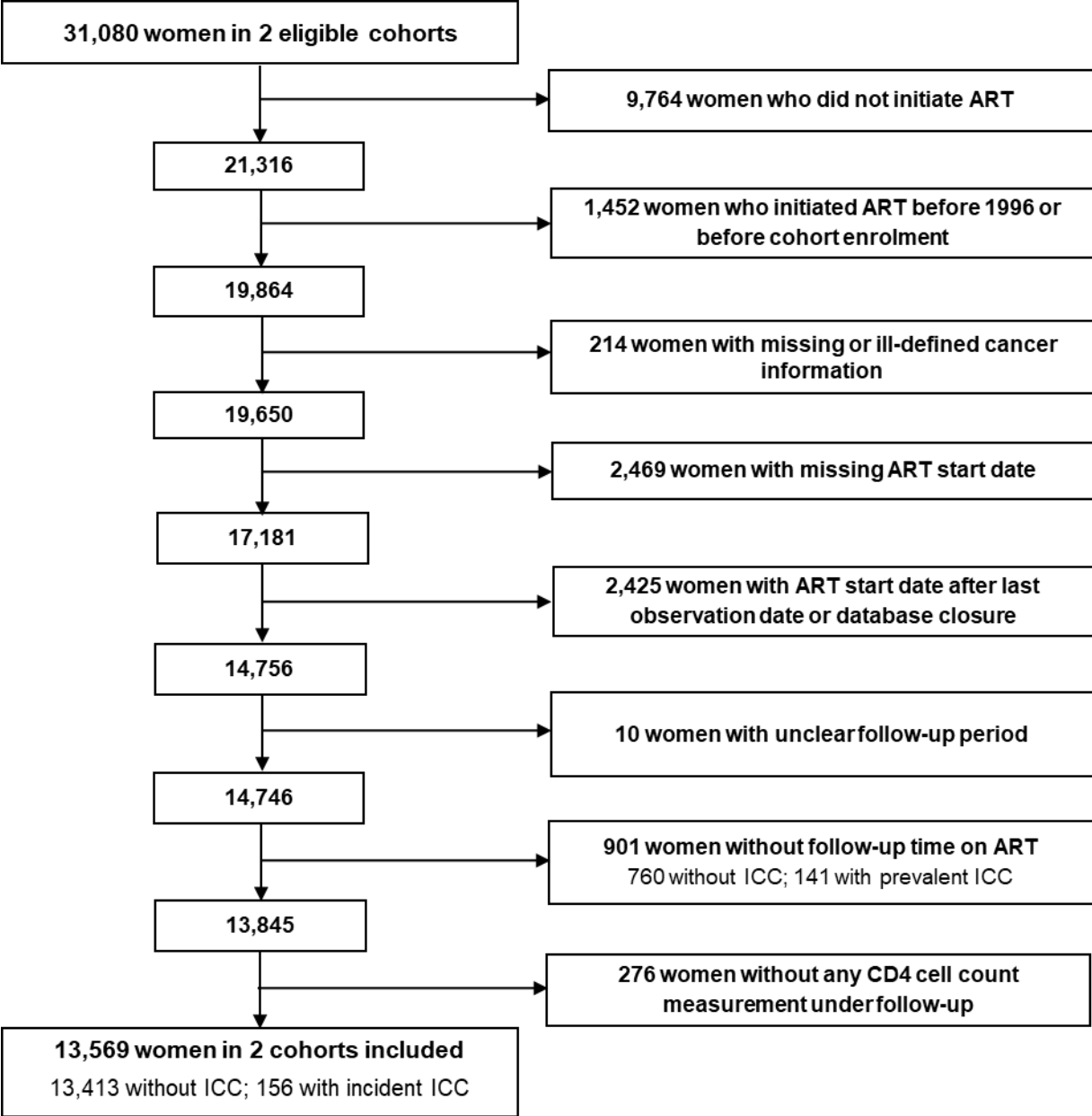
**Supplementary Figure S3:** Identification of study population for the North American region.



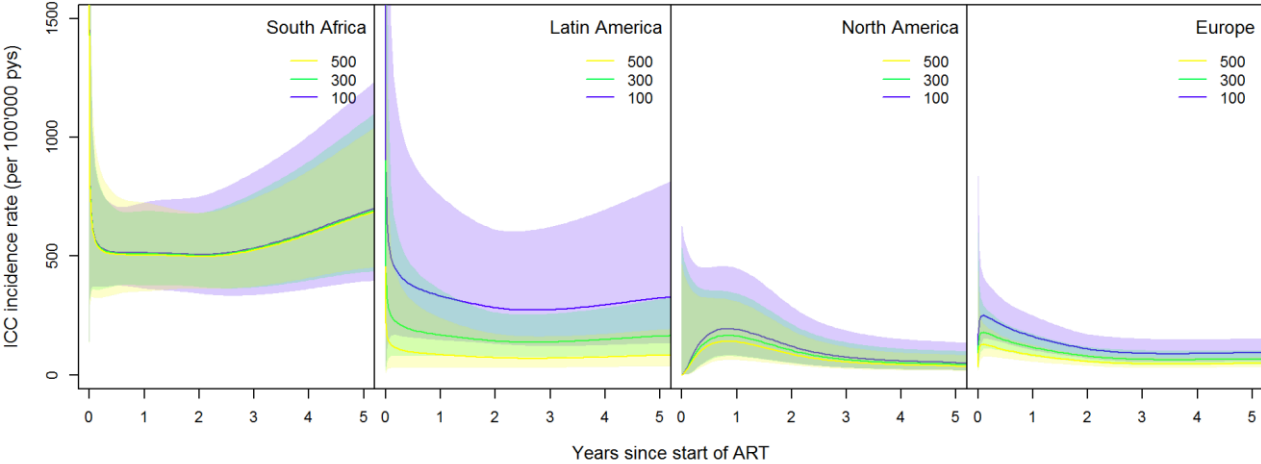
**Supplementary Figure S4:** Identification of study population for the Latin American region.



**Supplementary Figure S5:** Identification of study population for the South African region.



**Supplementary Figure S6:** ICC incidence rates by time since ART initiation and current CD4 cell count (cells/ $\mu$ l) predicted from the second adjusted model (sensitivity analysis) for women living with HIV who initiated an NNRTI-based first-line ART regimen between 2008-2014 at age 31-50 years.



ART, antiretroviral therapy; ICC, invasive cervical cancer; NNRTI, non-nucleoside reverse-transcriptase inhibitor.



**Supplementary Table S1:** Characteristics of women with incident ICC.

	<b>South Africa</b>	<b>Latin America</b>	<b>North America</b>	<b>Europe</b>
	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
<b>All ICC cases</b>	156 (100%)	17 (100%)	19 (100%)	164 (100%)
<b>Median time to ICC diagnosis (IQR) [years]</b>	1.7 (0.9-3.2)	2.6 (0.7-5.6)	1.7 (1.2-6.0)	2.2 (0.7-5.3)
<b>Median age at ICC diagnosis (IQR) [years]</b>	38.3 (33.5; 42.7)	33.0 (28.8; 43.4)	39.0 (29.6; 43.1)	39.7 (33.8; 45.4)
<b>Age at ICC diagnosis [years]</b>				
16-30	13 (8%)	5 (29%)	5 (26%)	16 (10%)
31-50	131 (84%)	10 (59%)	13 (68%)	124 (76%)
>50	12 (8%)	2 (12%)	1 (5%)	24 (15%)
<b>First-line ART regimen</b>				
NNRTI-based	150 (96%)	14 (82%)	3 (16%)	55 (34%)
PI-based	5 (3%)	3 (18%)	15 (79%)	103 (63%)
Other ART	1 (1%)	0 (0%)	1 (5%)	6 (4%)
<b>Year of ART initiation</b>				
1996-1998	0 (0%)	1 (6%)	10 (53%)	36 (22%)
1999-2003	0 (0%)	6 (35%)	6 (32%)	71 (43%)
2004-2007	114 (73%)	3 (18%)	3 (16%)	31 (19%)
2008-2014	42 (27%)	7 (41%)	0 (0%)	26 (16%)
<b>Median CD4 cell count at ICC diagnosis (IQR) [cells/<math>\mu</math>l]</b>	292 (170-450)	275 (190-406)	370 (200-586)	350 (183-523)
Women with missing CD4 cell count at ICC diagnosis	37 (24%)	6 (35%)	1 (5%)	23 (14%)
<b>Median HIV RNA at ICC diagnosis (IQR) [log<sub>10</sub> copies/ml]</b>	1.7 (1.7-1.7)	1.7 (1.6-3.3)	2.3 (2.3-2.8)	2.0 (1.7-3.7)
Women with missing HIV RNA at ICC diagnosis	51 (33%)	4 (24%)	1 (5%)	31 (19%)

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

**Supplementary Table S2: 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; sensitivity analysis excluding ICC cases diagnosed within the first three months after ART initiation.

Region	At 2 years		At 5 years	
	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Europe	1.00	1.00	1.00	1.00
North America	1.31 (0.71 - 2.41)	1.09 (0.55 - 2.15)	0.99 (0.49 - 2.01)	0.80 (0.37 - 1.74)
Latin America	1.81 (1.02 - 3.24)	1.94 (0.98 - 3.82)	2.32 (1.23 - 4.39)	2.42 (1.22 - 4.78)
South Africa	7.36 (5.52 - 9.83)	6.85 (4.60 - 10.19)	10.53 (7.08 - 15.67)	9.87 (5.89 - 16.53)

\* 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.

**Supplementary Table S3:** Sensitivity analysis of risk factors for incident ICC in women who have initiated ART, excluding ICC cases diagnosed within the first three months after ART initiation.

	<b>Hazard ratio* (95% CI)</b>
<b>CD4 cell count at ART initiation</b>	
per 100 cells/ $\mu$ l decrease	1.23 (1.12 - 1.34)
<b>Age at ART initiation [years]</b>	
16-30	1.00
31-50	1.32 (1.00 - 1.76)
>50	1.48 (0.94 - 2.33)
<b>First-line ART regimen</b>	
NNRTI-based	1.00
PI-based	1.07 (0.79 - 1.45)
Other ART	0.39 (0.16 - 0.97)
<b>Year of ART initiation</b>	
1996-1998	1.71 (1.01 - 2.90)
1999-2003	1.37 (0.88 - 2.13)
2004-2007	0.98 (0.69 - 1.39)
2008-2014	1.00

\* Adjusted for region, CD4 cell count at ART initiation, age, calendar year of ART start, 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

**Supplementary Table S4:** Sensitivity analysis of risk factors for incident ICC in women who have initiated ART, including current CD4 cell count instead of CD4 cell count at ART initiation.

	<b>Hazard ratio* (95% CI)</b>	<b>p-value for interaction**</b>
<b>Current CD4 cell count per 100 cells/<math>\mu</math>l decrease</b>		0.017
South Africa	1.00 (0.92 - 1.10)	
Latin America	1.41 (1.07 - 1.86)	
North America	1.08 (0.90 - 1.30)	
Europe	1.18 (1.10 - 1.27)	
<b>Age at ART initiation [years]</b>		0.055
16-30	1.00	
31-50	1.39 (1.07 - 1.81)	
>50	1.54 (1.02 - 2.32)	
<b>First-line ART regimen</b>		0.103
NNRTI-based	1.00	
PI-based	1.01 (0.77 - 1.33)	
Other ART	0.48 (0.23 - 1.00)	
<b>Year of ART initiation</b>		0.129
1996-1998	1.46 (0.92 - 2.32)	
1999-2003	1.14 (0.77 - 1.66)	
2004-2007	0.84 (0.62 - 1.13)	
2008-2014	1.00	

\* Adjusted for current CD4 cell count and its interaction with region, age, calendar year of ART start, and first-line ART regimen.

\*\* Derived from likelihood ratio test comparing the adjusted models 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

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