***Target Journal:*** *International Journal of Cancer*

**Title:** Cervical Cancer Risk and Impact of Pap-based Screening in HIV-positive Women on Antiretroviral Therapy in Johannesburg, South Africa

**Short title:** Cervical Cancer Risk in HIV-positive Women in Johannesburg, South Africa

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**Key words:** Cervical cancer, HIV, South Africa, cohort study, screening.

**Article category**: Cancer Epidemiology

**Meetings where this work was presented:**

- 21th International AIDS Conference; July 18-22, 2016; Durban, South Africa.

**Abbreviations used:**

AIDS; acquired immune deficiency syndrome; ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; HREC, Human Research Ethics Committee; ICC, invasive cervical cancer; IQR, interquartile range; LEEP, loop electrical excision procedure; NCR, National Cancer Registry; non-NNRTI, nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; Pap, Papanicolaou; PEPFAR, President's Emergency Plan for AIDS Relief; PI, protease inhibitor; pys, person-years; TLC, Themba Lethu Clinic; USAID, United States Agency for International Development ; WHO, World Health Organization.

**What's new?** (75 words, max. 75)

Data on invasive cervical cancer (ICC) incidence in HIV-positive women and the effect of cervical cancer screening in sub-Saharan Africa are scarce. This South African cohort analysis found that ICC incidence substantially decreased after the implementation of a Pap-based screening program and improved access to treatment of cervical lesions. However, ICC risk remained high in women who initiated ART at low CD4 cell counts. Patient-level monitoring of screening programs is essential to improve ICC prevention.

**Abstract (248 max. 250, unstructured)**

Data on invasive cervical cancer (ICC) incidence in HIV-positive women and the effect of cervical cancer screening in sub-Saharan Africa are scarce. We estimated i) ICC incidence rates in women (≥18 years) who initiated antiretroviral therapy (ART) at the Themba Lethu Clinic (TLC) in Johannesburg, South Africa, between 2004-2011; and ii) the effect of a Pap-based screening program. We included 10,640 women; median age at ART initiation: 35 years (interquartile range [IQR] 30-42), median CD4 count at ART initiation: 113 cells/µl (IQR 46-184). During 27,257 person-years (pys), 138 women were diagnosed with ICC; overall incidence rate: 506/100,000 pys (95% CI 428-598). The ICC incidence rate was highest (615/100,000 pys) in women who initiated ART before cervical cancer screening became available in 04/2005, and was lowest (260/100,000 pys) in women who initiated ART from 01/2009 onwards when the cervical cancer screening program and access to treatment of cervical lesions was expanded (adjusted hazard ratio [aHR] 0.42, 95% confidence interval [CI] 0.20-0.87). Advanced HIV/AIDS stage (4 versus 1, aHR 1.95, 95% CI 1.17-3.24) and middle age at ART initiation (36-45 versus 18-25 years, aHR 2.51, 95% CI 1.07-5.88) were risk factors for ICC. The ICC incidence rate substantially decreased with the implementation of a Pap-based screening program and improved access to treatment of cervical lesions. However, the risk of developing ICC after ART initiation remained high. To inform and improve ICC prevention and care for HIV-positive women in sub-Saharan Africa, implementation and monitoring of cervical cancer screening programs are essential.

## Introduction

Invasive cervical cancer (ICC) is an AIDS-defining malignancy associated with high-risk types of human papillomavirus (HPV) infection.[1] HIV-positive women have a higher risk of co-infection with high-risk HPV types, HPV reactivation, persistence of cytological abnormalities and more rapid progression to ICC.[2–8] In South Africa, where one in every four adult women (15-49 years) have HIV,[9] ICC is the second most common cancer in women in the general population and the leading cause of cancer-related deaths.[10]

The effect of antiretroviral therapy (ART) on the incidence of cervical lesions and ICC in HIV-positive women remains unclear.[11–14] On one hand, early initiation of ART may reduce the risk of coinfection with high-risk HPV types.[15] On the other hand, ART might lead to higher ICC incidence rates due to lower competing mortality from other HIV-related causes.[11] Therefore, effective cervical cancer screening programs are essential to lower ICC-related morbidity and mortality in HIV-positive women.[16] Because of the increased risk of developing ICC, more frequent cervical cancer screening is recommended for HIV-positive than for HIV-negative women.[17,18] To inform cervical cancer screening programs for HIV-positive women in South Africa, data on ICC burden, associated risk factors, and the effect of screening programs on ICC risk in this specific population are needed. Whereas some ICC incidence rate estimates are available for HIV-positive women in sub-Saharan Africa, ranging from 8/100,000 pys to 259/100,000 pys,[19–22] data on risk factors and the effect of cervical cancer screening on ICC risk are scarce for the African setting. Studies examining the effect of cervical cancer screening at the patient-level often do not have enough power to detect changes in ICC incidence rates.[13,15] However, relevant information can also be obtained from using precancerous lesions as an endpoint.

We estimated ICC incidence rates in HIV-positive women who initiated ART at the Themba Lethu Clinic (TLC) in Johannesburg, South Africa, identified risk factors for developing ICC in these women, and assessed the effect of the introduction and expansion of a Papanicolaou (Pap) smear based cervical cancer screening program on ICC incidence rates.

## Methods

### Study site and data sources

The TLC in Johannesburg, South Africa, was established in 1992 to provide care for HIV-positive adults living in the area. It is a government clinic, but also receives financial support from Right to Care, a South African non-profit organization, which is partly funded by the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR) program. Since 2004, the TLC cohort prospectively captures clinical, demographic, laboratory and treatment data collected as part of routine care.[23] This routine data is captured at enrolment and each follow-up visit and is stored electronically. Follow-up visits are typically scheduled one, three, six, and 12 months after ART start and yearly thereafter. Since April 2005 HIV-positive women are screened for abnormal cytological findings of the cervix using conventional Pap tests as liquid based cytology is not available in the South African public health sector. In 2009, the Pap-based cervical cancer screening program established at the TLC was extended beyond the inception site to further HIV clinics in the area, and loop electrical excision procedure (LEEP) became available for treatment of high-grade cervical lesions in screened women. In line with the guidelines of the South African National Department of Health,[18] Pap tests are supposed to be repeated every three years if cytology results are normal and after one year if a low-grade cervical squamous intraepithelial lesion is detected in HIV-positive women. Women with high-grade intraepithelial lesions are supposed to be referred for colposcopy. In 2011, data from the TLC cohort were linked to the South African National Cancer Registry (NCR) database to complete cancer case recording for patients enrolled in the TLC cohort. The NCR is pathology-based and collects information on histologically, cytologically or haematologically confirmed cancer cases from both public and private laboratories all over South Africa. The record linkage was probabilistic and based on first name, second name, surname, date of birth, and gender. Data from the cancer registry were available up to August 2011. To minimize the risk of mismatches cancer cases identified through the probabilistic record linkage with the NCR were cross-checked for plausibility with patient files from the TLC. The TLC cohort has an on-going ethics approval (M140201)

from the Human Research Ethics Committee (Medical) (HREC) of the University of the Witwatersrand to analyse routine clinical data, and this approval is renewed annually. The record linkage between the TLC cohort database and the NCR in South Africa was based on an additional HREC-approved protocol (M110324). Ethical approval was obtained specifically for the current project from the HREC (M150215), the London School of Hygiene and Tropical Medicine (LSHTM) MSc Research Ethics Committee (Ref. 8948), and the Cantonal Ethics Committee (KEK) Bern (Ref. 028/15).

**Inclusion criteria and definitions**

We included all HIV-positive women aged 18 years or older who initiated ART at the TLC between April 2004 when the national ART program was initiated in South Africa and August 2011 when the record linkage with the NCR was performed. Women who started ART before enrolment into the cohort and women without follow-up time on ART, including those diagnosed with ICC before starting ART, were excluded. Database closure was set at time of record linkage with the NCR (31st August 2011). Calendar time was categorized into three periods to reflect the initiation and extension of Pap-based cervical cancer screening, i.e. 04/2004-03/2005 without cervical cancer screening at TLC, 04/2005-12/2008 with Pap-based cervical cancer screening at TLC, and 01/2009-08/2011 when Pap-based cervical cancer screening was extended beyond TLC and LEEP became available. ART was defined as a regimen of at least three antiretroviral drugs of any of the following drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or protease inhibitors (PIs). Regimens consisting of two NRTIs and one NNRTI were classified as NNRTI-based, regimens consisting of two NRTIs and one PI (with or without ritonavir as a booster) were classified as PI-based. Women were assumed to stay on ART once started. CD4 cell counts at ART initiation were defined as the measurement closest to the date of ART initiation, within 90 days before to seven days after ART initiation. Nadir CD4 was defined as the lowest ever measured CD4 cell count before ICC diagnosis. ICC cases diagnosed before or at start of ART were excluded as prevalent cases, whereas ICC cases diagnosed after ART initiation were analysed as incident cases.

**Statistical analyses**

We calculated ICC incidence rates by dividing the number of women who were diagnosed with ICC after ART initiation by the total person-time at risk. Time at risk was measured from ART initiation to ICC diagnosis, last follow-up visit, death, or database closure, whichever occurred first. We calculated ICC incidence rates for the whole observation time, but also separately for different time periods after ART initiation (0 to 1 year, >1 to 3 years, and >3 years after ART initiation). We computed age-standardized ICC incidence rates using the world standard population proposed by Segi[24] and adapted by Doll and colleagues.[25] As our study population did not include children and only few elderly women, we assumed that all women aged ≥60 years had the same ICC incidence rate and that children had an ICC incidence rate of zero. In a sensitivity analysis, we restricted the world standard population to adults. We examined potential risk factors for incident ICC using crude and adjusted Cox proportional hazards models. We explored the following potential risk factors: age at ART initiation (18-25 years, 26-35 years, 36-45 years, ≥46 years), current (time-updated) age (18-25 years, 26-35 years, 36-45 years, ≥46 years), employment status (unemployed versus employed), body mass index (BMI) at ART start (<18.5, 18.5-24.9, ≥25 kg/m2), smoking status (never smoked/ever smoked), first-line ART regimen (NNRTI-based, PI-based, other ART), calendar period of ART initiation (04/2004-03/2005, 04/2005-12/2008, 01/2009-08/2011), calendar period of follow-up (04/2004-03/2005, 04/2005-12/2008, 01/2009-08/2011), WHO clinical stage of HIV/AIDS at ART initiation (1, 2, 3, 4), CD4 cell count at ART start (<50, 50-99, 100-199, ≥200 cells/µl), nadir CD4 (<50, 50-99, 100-199, ≥200 cells/µl), current (time-updated) CD4 cell count (<100, 100-199, 200-349, 350-499, ≥500 cells/µl), and haemoglobin at ART initiation (<10.0, 10.0-11.9, ≥12.0 g/dl). As women with prevalent ICC were excluded from the analysis, WHO stage 4 at ART initiation was based on other stage-defining co-morbidities than ICC. We also included CD4 cell counts as spline variables in the model. The multivariable Cox model included all variables that were significantly or borderline significantly associated with ICC risk in univariable analyses, that is age at ART initiation, first-line ART regimen, calendar period of ART initiation, and WHO clinical stage of HIV/AIDS at ART initiation. The significance level was set at p-value < 0.05 for all

hypothesis tests. In sensitivity analyses we excluded ICC cases diagnosed within six months after ART initiation and women with less than six months of follow-up to reduce potential misclassification of prevalent ICC cases as incident ICC cases, and we used multiple imputations for missing data on CD4 cell counts and WHO stage on HIV/AIDS at ART initiation. We used predictive mean matching and chained equations to create 20 imputed datasets. Results are presented as percentages, medians with interquartile ranges (IQR), incidence rates per 100,000 pys with 95% confidence intervals (CIs), or hazard ratios (HRs) with 95% CIs. All analyses were done in Stata 13.1 (Stata Corporation, College Station, Texas, USA).

## Results

### Study population

The TLC dataset included information on 13,383 HIV-positive women aged 18 years or older who initiated ART at the TLC between 1st April 2004 and 31st August 2011. Of these we excluded 1,936 women who started ART before enrolment into the cohort. Another 807 women were excluded for reasons detailed in Figure 1. Excluded women were slightly younger (median age: 33 years versus 35 years) and more likely to receive PI-based first-line ART regimens (14% versus 8%) than included women. Data on WHO clinical HIV/AIDS stage and CD4 cell counts at ART initiation were missing for the majority of excluded women (68% and 43%, respectively), but for less than 15% of included women, and could therefore not be compared.

We included data on 10,640 women; median age at ART initiation was 35 years (IQR 30-42 years), median CD4 cell count at ART initiation was 113 cells/µl (IQR 46-184 cells/µl). Over calendar period, the median CD4 cell count at ART initiation increased from 82 cells/µl (IQR 36-143 cells/µl) in 04/2005-03/2005 to 140 cells/µl (IQR 66-210 cells/µl) in 01/2009-08/2011. About 10% of the included women (n=1,021) initiated ART in WHO clinical stage 4, and most women (n=9,785; 92%) received an NNRTI-

based first-line regimen. About half of the women were unemployed (53%, n=5,646) and the majority had never smoked (83%, n=8,823).

**ICC incidence rates and risk factors**

During a total of 27,257 pys, 138 women were diagnosed with ICC for an overall ICC incidence rate of 506/100,000 pys (95% CI 428-598). The age-standardized ICC incidence rate was 273/100,000 pys (95% CI 177-420) when including children and 396/100,000 (95% CI 256-614) when excluding children. Median follow-up time after ART initiation was 2.1 years (IQR 0.7-4.1 years), and median time to ICC diagnosis after ART start was 1.8 years (IQR 0.9-3.2 years). The ICC incidence rate did not change over time after ART initiation (Figure 2). The ICC incidence rate declined over calendar time of ART initiation: it was highest (615/100,000 pys) in women who initiated ART before Pap-based screening became available at TLC in April 2005, and it was lowest (260/100,000 pys) in women who initiated ART from 2009 onwards when LEEP became available and Pap-based cervical cancer screening was expanded beyond TLC to other HIV clinics in the area, see table 1. No decrease in ICC incidence rates was apparent when we looked at calendar period of follow-up instead of calendar period of ART initiation. When we excluded the first six months of follow-up after ART initiation in a sensitivity analysis, the ICC incidence rate remained similar in the earlier calendar periods of ART initiation, but declined to 69/100,000 pys in the most recent calendar period of ART initiation (Supplementary table S1).

In univariable analyses, the risk of developing ICC was associated with calendar period of ART initiation ($p = 0.011$), age at ART initiation ($p = 0.031$), first-line ART regimen ($p = 0.003$), and WHO clinical stage of HIV/AIDS at ART initiation ($p = 0.059$), see table 1. However, CD4 cell count at ART initiation, nadir CD4 and current CD4 cell count had no effect on ICC risk in our analyses, neither as categorical variables nor as spline variables (data on file). We also did not find an association between ICC risk and calendar period of follow-up, employment status, BMI at ART initiation, smoking status, and haemoglobin at ART initiation.

In adjusted analyses, the risk of developing ICC decreased over calendar period of ART initiation: women who initiated ART from 2009 onwards had a 58% lower risk of developing ICC than women who initiated ART before April 2005 (adjusted HR 0.42, 95% CI 0.20-0.87). When we excluded the first six months of follow-up after ART initiation and all ICC cases diagnosed within this period, ICC risk was 89% lower (adjusted HR 0.11, 95% CI 0.03-0.46). The other HRs for developing ICC remained similar (Supplementary table S1). Advanced WHO clinical stage of HIV/AIDS at ART initiation (stage 4 versus 1, adjusted HR 1.95, 95% CI 1.17-3.24) was a risk factor for incident ICC, and women who initiated ART at the age of 36-45 years were at highest risk of developing ICC (36-45 years versus 18-25 years, adjusted HR 2.51, 95% CI 1.07-5.88). A similar pattern was observed for current age with younger and older women having a lower risk of developing ICC compared to women aged 36-45 years (data on file). Women with PI-based first-line regimens (97% lopinavir/ritonavir) tended to have a lower risk of developing ICC than women who received a standard NNRTI-based first-line regimen (adjusted HR 0.54, 95% CI 0.22-1.34). Using multiple imputations for missing data on CD4 cell counts and WHO clinical stage of HIV/AIDS at ART initiation confirmed the findings of the complete cases analysis (Supplementary table 2).

## Discussion

The risk of developing ICC in women who initiated ART at the TLC in Johannesburg, South Africa, declined over calendar time of ART initiation with the introduction and expansion of Pap-based cervical cancer screening and treatment of cervical lesions. However, the ICC incidence rate in HIV-positive women on ART remained high even after the expansion of Pap-based cervical cancer screening to other HIV clinics in the area. We found that advanced WHO clinical stage of HIV/AIDS at ART initiation was a risk factor for developing ICC. In contrast, time since ART initiation and nadir, baseline, or current CD4 cell counts were not associated with the risk of developing ICC.

This study is one of the first to describe ICC incidence rates along with associated risk factors in HIV-positive women who initiated ART in sub-Saharan Africa, and the first one to evaluate the effect of the introduction of a Pap-based cervical cancer screening program on ICC incidence rates in this setting. It is based on prospectively collected routine clinical data, and ICC ascertainment was improved through record linkage with the South African NCR. However, several limitations need to be addressed. Even after the record linkage with the pathology-based NCR, ascertainment of ICC cases is likely to be incomplete, resulting in an underestimation of the ICC risk in women who initiated ART. Lag times in cancer registration at the NCR might lead to some under-reporting of ICC cases in more recent calendar periods. The results we report for HIV-positive women attending one urban ART program in South Africa might not necessarily be generalizable to all HIV-positive women initiating ART in South Africa or to other ART programs with different cervical cancer screening practices. Cervical cancer screening and treatment status at patient-level was not available, and therefore we could not assess the effect of Pap-based cervical cancer screening on ICC incidence rates directly. Data on several potentially relevant risk factors like HIV RNA load, number of pregnancies, contraceptive use, number of sexual partners, and condom use, were very limited or not available, and could therefore not be analysed. We assumed that women remained on ART once initiated and did not consider treatment interruptions and terminations. ICC incidence rates in women who are fully adherent to ART might be lower than what we report.

We found that the ICC incidence rate in our cohort decreased over calendar periods of ART initiation with the introduction of a screening program and early treatment of cervical lesions. We are not aware of other studies assessing ICC incidence rates before and after the introduction of a cervical cancer screening program in an ART program. However, Shiels and colleagues showed that in HIV-positive women in the United States yearly ICC incidence rates declined steeply in the early 1990's before the advent of ART.[26] This decline is most likely attributable to cervical cancer screening and improved treatment of pre-cancerous cervical lesions.[27] Other studies in HIV-positive women, on the other hand, showed increasing ICC incidence rates over calendar periods.[28–30]

Our study found a very high overall ICC incidence rate of more than 500/100,000 pys in HIV-positive women who initiated ART. Few other studies reported similarly high ICC incidence rates in HIV-positive women,[26,28,31] but most studies found substantially lower ICC incidence rates.[19–22,29,32–36] For example, in a cohort of regularly Pap-screened HIV-positive women in the United States, the ICC incidence rate was as low as 12/100,000 pys.[36] Whereas well-established systematic screening programs might partly explain the lower ICC incidence rates in HIV-positive women living in high-income countries, the very low ICC incidence rates found in three sub-Saharan African record linkage studies are likely to be underestimations.[19–21] The more limited access to pathology services in Nigeria, Uganda, and Malawi compared to South Africa might have resulted in more extensive under-diagnosis and under-reporting of ICC cases.[37] In general, ICC incidence rate estimates across studies need to be compared cautiously due to different study populations, settings, calendar periods, and study designs.

Immunodeficiency measured as low CD4 cell count is the most extensively studied risk factor for ICC in HIV-positive women, and its impact on ICC risk remains controversial. We and others did not find an association with ICC risk,[29,38] whereas some studies showed an increased ICC risk with lower CD4 cell counts at cohort enrolment[33] or during follow-up.[34] Interestingly, we found that advanced WHO clinical stage of HIV/AIDS as a measure of immunodeficiency at ART initiation was a risk factor for developing ICC, but Mbulaiteye and colleagues did not find such an association.[20] As in other studies, we also observed that ICC risk was highest in middle-aged women.[20,33,34] In our analysis, women who received PI-based regimens tended to have a lower risk of developing ICC than women who received a standard NNRTI-based regimen. In vitro studies have suggested that some PIs might have anti-tumour effects against cervical cancer cells.[39,40] However, as the treatment allocation was not randomized in our study, this finding should be interpreted with caution.

Before cervical cancer screening was introduced at TLC ICC incidence rates in HIV-positive women who had initiated ART were very high. After the introduction of cervical cancer screening and early treatment of cervical lesions at the TLC and expansion to other HIV clinics in the area ICC risk declined. We did not observe a decline in ICC incidence rates by time since ART initiation. However, most women

in our cohort initiated ART at low CD4 cell counts, and the follow-up time of our study might not have been long enough to detect a protective effect of ART on ICC development.[15] Besides efforts to grant universal access to prompt ART initiation, effective and wide-spread cervical cancer screening programs are needed to lower ICC-related morbidity and mortality. Different screening approaches including Pap smears, HPV testing, and visual inspection with acetic acid and Lugol's iodine are available.[41] To determine the best screening approach for a given setting, available resources and cost-effectiveness need to be taken into account.[42] Irrespective of the screening method chosen, adequate infrastructure, trained personnel, and access to early treatment of cervical lesions are essential to ensure effectiveness.[43] In addition, rigorous monitoring of cervical cancer screening programs is needed to continuously improve and maintain patient outcomes.[43]

Large-scale studies analysing temporal trends in ICC incidence rates are important because they have sufficient power to evaluate ICC directly as the outcome of interest. However, without patient-level data on screening and treatment of cervical lesions, it is not possible to determine the extent to which interventions such as a screening program have directly impacted on outcomes, nor to understand observed ICC incidence rates in context, and to prioritize targets for further intervention. Therefore, observational HIV cohorts routinely collecting patient-level data on cervical cancer screening status and treatment of cervical lesions can offer critical evidence towards understanding ICC and should be prioritised in future evaluations.

With the implementation of a Pap-based screening program and improved access to treatment of cervical lesions the incidence rate of ICC substantially decreased in HIV-positive women who initiated ART. However, the risk of developing ICC after ART initiation remained high. To inform ICC prevention and care for HIV-positive women, implementation and thorough monitoring of cervical cancer screening programs in sub-Saharan Africa are essential.

**Acknowledgements**

We thank the directors and staff of Themba Lethu Clinic and Right to Care, the nongovernmental organization supporting the study site through a partnership with the US Agency for International Development (USAID). We also would like to acknowledge colleagues at the National Health Laboratory Service and the National Cancer Registry, and Marcel Zwahlen (Institute of Social and Preventive Medicine, University of Bern) for statistical advice. This work was supported by the Swiss National Science Foundation [Ambizione-PROSPER PZ00P3_136620 to J.B.], the USAID under the terms of agreement, USAID-674-A-12-00029, and 674-A-00-08-00007-00, and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U01AI069924 (PI: Egger and Davies). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

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**Table 1: Invasive cervical cancer (ICC) incidence rates per 100,000 person-years and hazard ratios for developing ICC in HIV-positive women who initiated ART.**

| | Patients (N) | Person-years | Cases (N) | Incidence rate (95% CI) | Crude HR (95% CI) | Adjusted HR *† (95% CI) |
|---|---|---|---|---|---|---|
| **Overall** | 10,640 | 27,257 | 138 | 506 (428-598) | - | - |
| **Calendar period of ART start** | | | | | | |
| 04/2004-03/2005 | 1,236 | 5,853 | 36 | 615 (444-853) | 1.00 | 1.00 |
| 04/2005-12/2008 | 5,296 | 16,794 | 90 | 536 (436-659) | 0.81 (0.54-1.20) | 0.82 (0.53-1.26) |
| 01/2009-08/2011 | 4,108 | 4,609 | 12 | 260 (148-458) | 0.37 (0.19-0.74) | 0.42 (0.20-0.87) |
| **Calendar period of follow-up** | | | | | | |
| 04/2004-03/2005 | - | 492 | 0 | 0 (0-752) | - | - |
| 04/2005-12/2008 | - | 11,394 | 64 | 562 (440-718) | 1.00 | - |
| 01/2009-08/2011 | - | 15,371 | 74 | 481 (383-605) | 0.84 (0.58-1.21) | - |
| **Time since ART start** | | | | | | |
| 0-1 year | - | 8,689 | 41 | 472 (347-641) | - | - |
| >1-3 years | - | 10,936 | 56 | 512 (394-665) | - | - |
| >3 years | - | 7,633 | 41 | 537 (396-730) | - | - |
| **Age at ART start** | | | | | | |
| 18-25 years | 1,064 | 2,695 | 6 | 223 (100-496) | 1.00 | 1.00 |
| 26-35 years | 4,693 | 12,610 | 64 | 508 (397-648) | 2.28 (0.99-5.26) | 1.93 (0.83-4.48) |
| 36-45 years | 3,290 | 8,293 | 53 | 639 (488-837) | 2.89 (1.24-6.72) | 2.51 (1.07-5.88) |
| ≥ 46 years | 1,593 | 3,658 | 15 | 410 (247-680) | 1.86 (0.72-4.79) | 1.35 (0.50-3.63) |
| **Employment status** | | | | | | |
| Unemployed | 5,646 | 15,064 | 81 | 538 (432-669) | 1.00 | - |
| Employed | 4,765 | 11,801 | 55 | 466 (358-607) | 0.86 (0.61-1.22) | - |
| Missing | 229 | 391 | 2 | - | - | - |
| **BMI at ART start [kg/m$^2$]** | | | | | | |
| < 18.5 | 1,432 | 3,347 | 15 | 448 (270-743) | 1.00 | - |
| 18.5-24.9 | 4,899 | 13,252 | 67 | 506 (398-642) | 1.13 (0.65-1.98) | - |
| ≥ 25.0 | 3,250 | 8,440 | 46 | 545 (408-728) | 1.22 (0.68-2.19) | - |
| Missing | 1,059 | 2,218 | 10 | - | - | - |
| **Smoking status** | | | | | | |
| Never smoked | 8,823 | 23,003 | 117 | 509 (424-610) | 1.00 | - |
| Ever smoked | 506 | 1,192 | 7 | 587 (280-1232) | 1.15 (0.54-2.47) | - |
| Missing | 1,311 | 3,062 | 14 | - | - | - |

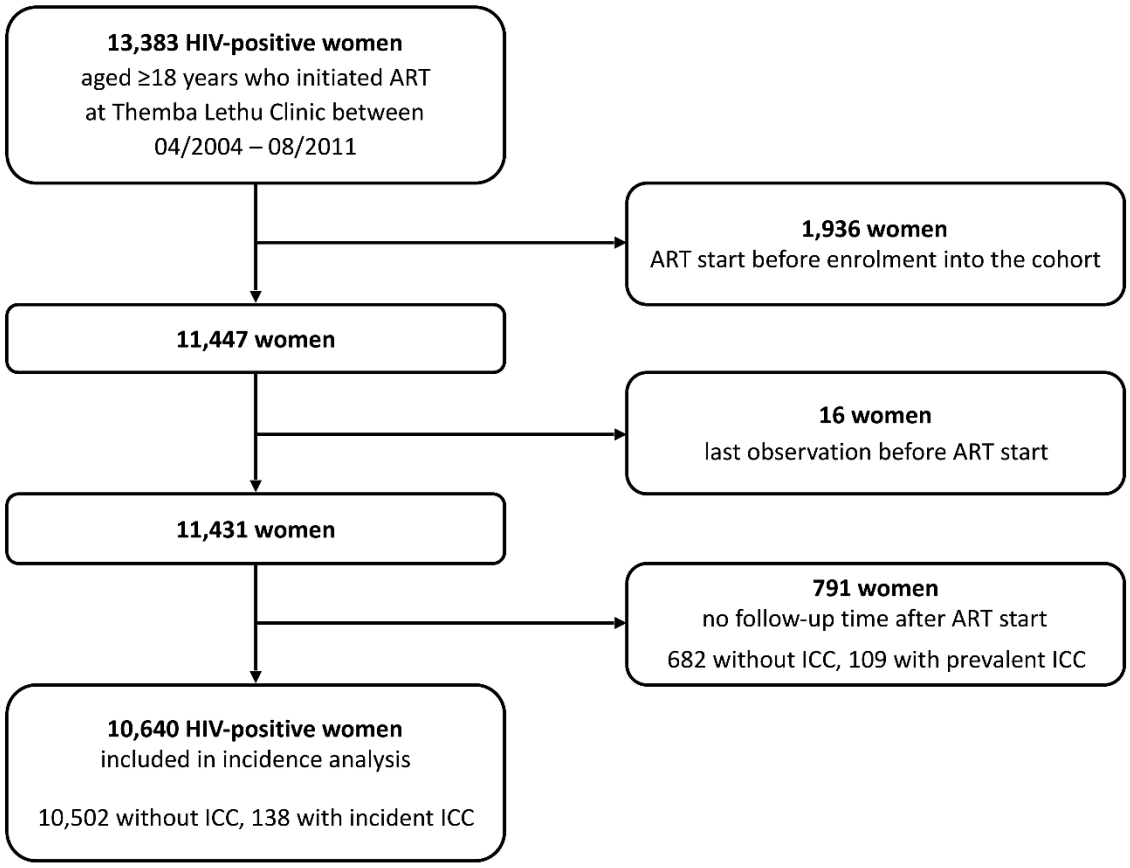
| | | | | | | |
|---|---|---|---|---|---|---|
| **First-line ART regimen** | | | | | | |
| NNRTI-based | 9,785 | 24,637 | 129 | 524 (441-622) | 1.00 | 1.00 |
| PI-based | 824 | 2,535 | 6 | 237 (106-527) | 0.45 (0.20-1.1) | 0.54 (0.22-1.34) |
| Other ART | 31 | 85 | 3 | 3533 (1139-10953) | 6.75 (2.15-21.21) | 7.85 (1.93-32.03) |
| **WHO stage of HIV/ AIDS at ART start** | | | | | | |
| 1 | 3,878 | 11,128 | 53 | 476 (364-623) | 1.00 | 1.00 |
| 2 | 1,738 | 3,999 | 17 | 425 (264-684) | 0.90 (0.52-1.55) | 0.88 (0.51-1.53) |
| 3 | 2,534 | 6,929 | 35 | 505 (363-704) | 1.06 (0.69-1.62) | 0.99 (0.64-1.52) |
| 4 | 1,021 | 2,208 | 21 | 951 (620-1459) | 1.99 (1.20-3.31) | 1.95 (1.17-3.24) |
| Missing | 1,469 | 2,992 | 12 | - | - | - |
| **CD4 cell count at ART start [cells/µl]** | | | | | | |
| < 50 | 2,522 | 6,644 | 36 | 542 (391-751) | 1.00 | - |
| 50-99 | 1,777 | 4,937 | 25 | 506 (343-749) | 0.94 (0.56-1.56) | - |
| 100-199 | 3,430 | 8,981 | 48 | 534 (403-709) | 0.99 (0.64-1.52) | - |
| ≥ 200 | 1,857 | 3,904 | 19 | 487 (310-763) | 0.91 (0.52-1.58) | - |
| Missing | 1,054 | 2,790 | 10 | - | - | - |
| **CD4 nadir [cells/µl]** | | | | | | |
| < 50 | 2,947 | 7,840 | 47 | 599 (450-798) | 1.00 | - |
| 50-99 | 2,092 | 5,887 | 26 | 442 (301-649) | 0.74 (0.46-1.19) | - |
| 100-199 | 3,932 | 10,307 | 50 | 485 (368-640) | 0.81 (0.54-1.21) | - |
| ≥ 200 | 1,594 | 3,166 | 15 | 474 (286-786) | 0.79 (0.44-1.42) | - |
| Missing | 75 | 57 | 0 | - | - | - |
| **Current CD4 cell count [cells/µl]** | | | | | | |
| < 100 | - | 2,429 | 15 | 618 (372-1024) | 1.00 | - |
| 100-199 | - | 4,379 | 21 | 480 (313-735) | 0.81 (0.41-1.60) | - |
| 200-349 | - | 7,621 | 43 | 564 (418-761) | 0.92 (0.47-1.78) | - |
| 350-499 | - | 6,189 | 26 | 420 (286-617) | 0.65 (0.31-1.35) | - |
| ≥ 500 | - | 6,182 | 31 | 501 (353-713) | 0.75 (0.36-1.58) | - |
| Missing | - | 457 | 2 | - | - | - |
| **Haemoglobin at ART start [g/dl]** | | | | | | |
| < 10.0 | 2,589 | 6,014 | 27 | 449 (308-655) | 1.00 | - |
| 10.0-11.9 | 3,561 | 9,288 | 49 | 528 (399-698) | 1.18 (0.74-1.89) | - |
| ≥ 12.0 | 3,570 | 9,512 | 52 | 547 (417-717) | 1.22 (0.77-1.95) | - |
| Missing | 920 | 2,442 | 10 | - | - | - |

* Restricted to 9,171 women with available WHO clinical stage of HIV/AIDS at ART start.

† Adjusted for age, calendar period of ART start, first-line ART regimen, and WHO clinical stage of HIV/AIDS.

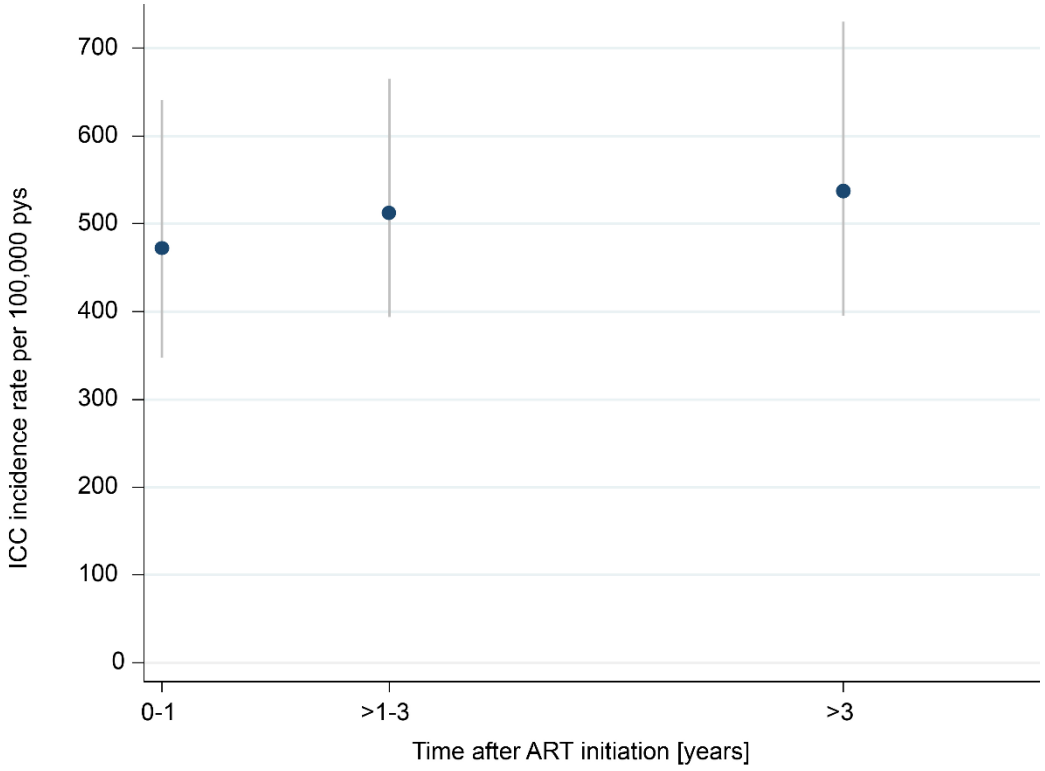
ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; ICC, invasive cervical cancer; IQR, interquartile range; HR, hazard ratio; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; WHO, World Health Organization.

**Figure 1:** Identification of study population. The flow diagram shows the number of included and excluded women.




ART, antiretroviral therapy; ICC, invasive cervical cancer.

**Figure 2:** Invasive cervical cancer incidence rates with 95% confidence intervals by time since initiation of antiretroviral therapy.




ART, antiretroviral therapy; ICC, invasive cervical cancer; pys; person-years.

**Cervical Cancer Risk and Impact of Pap-based Screening in HIV-positive Women on Antiretroviral Therapy in Johannesburg, South Africa**

Eliane Rohner, Mazvita Sengayi, Bridgette Goeieman, Pamela Michelow, Cindy Firnhaber, Mhairi Maskew, Julia Bohlius

## Supplementary material

- **Supplementary Table S1: Invasive cervical cancer (ICC) incidence rates per 100,000 person-years and hazard ratios for developing ICC in HIV-positive women on ART.** Sensitivity analysis excluding all women with less than six months of follow-up after ART initiation, including those diagnosed with ICC within that time period.
- **Supplementary Table S2: Hazard ratios for developing ICC in HIV-positive women who initiated ART.** Sensitivity analysis based on multiply imputed dataset.

**Supplementary Table S1: Invasive cervical cancer (ICC) incidence rates per 100,000 person-years and hazard ratios for developing ICC in HIV-positive women on ART.** Sensitivity analysis excluding all women with less than six months of follow-up after ART initiation, including those diagnosed with ICC within that time period.

| | Patients (N) | Person-years | Cases (N) | Incidence rate (95% CI) | Crude HR (95% CI) | Adjusted HR *† (95% CI) |
|---|---|---|---|---|---|---|
| **Overall** | 8,560 | 22,588 | 112 | 496 (412-597) | - | - |
| **Calendar period of ART start** | | | | | | |
| 04/2004-03/2005 | 1,102 | 5,278 | 35 | 663 (476-924) | 1.00 | 1.00 |
| 04/2005-12/2008 | 4,513 | 14,414 | 75 | 520 (415-652) | 0.72 (0.47-1.08) | 0.69 (0.44-1.07) |
| 01/2009-08/2011 | 2,945 | 2,896 | 2 | 69 (17-276) | 0.09 (0.02-0.39) | 0.11 (0.03-0.46) |
| **Calendar period of follow-up** | | | | | | |
| 04/2004-03/2005 | - | 64 | 0 | - | - | - |
| 04/2005-12/2008 | - | 9,020 | 49 | 543 (411-719) | 1.00 | - |
| 01/2009-08/2011 | - | 13,504 | 63 | 467 (364-597) | 0.82 (0.54-1.23) | - |
| **Time since ART start** | | | | | | |
| 0.5-1 year | - | 4,020 | 15 | 373 (225-619) | - | - |
| >1-3 years | - | 10,936 | 56 | 512 (394-665) | - | - |
| >3 years | - | 7,633 | 41 | 537 (396-730) | - | - |
| **Age at ART start** | | | | | | |
| 18-25 years | 826 | 2,238 | 5 | 223 (93-537) | 1.00 | 1.00 |
| 26-35 years | 3,807 | 10,539 | 54 | 512 (392-669) | 2.30 (0.92-5.75) | 1.94 (0.77-4.89) |
| 36-45 years | 2,669 | 6,844 | 43 | 628 (466-847) | 2.83 (1.12-7.15) | 2.52 (0.99-6.42) |
| ≥ 46 years | 1,258 | 2,967 | 10 | 337 (181-626) | 1.53 (0.52-4.48) | 1.12 (0.36-3.47) |
| **Employment status** | | | | | | |
| Unemployed | 4,491 | 12,598 | 68 | 540 (426-685) | 1.00 | - |
| Employed | 3,914 | 9,690 | 42 | 433 (320-587) | 0.80 (0.55-1.18) | - |
| Missing | 155 | 300 | 2 | - | - | - |
| **BMI at ART start [kg/m$^2$]** | | | | | | |
| < 18.5 | 1,040 | 2,756 | 13 | 472 (274-813) | 1.00 | - |
| 18.5-24.9 | 4,063 | 11,062 | 54 | 488 (374-637) | 1.04 (0.57-1.90) | - |
| ≥ 25.0 | 2,706 | 6,979 | 37 | 530 (384-732) | 1.13 (0.60-2.13) | - |
| Missing | 751 | 1,792 | 8 | - | - | - |
| **Smoking status** | | | | | | |
| Never smoked | 7,184 | 19,104 | 96 | 502 (411-614) | 1.00 | - |
| Ever smoked | 378 | 977 | 5 | 512 (213-1230) | 1.02 (0.41-2.51) | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Missing | 998 | 2,507 | 11 | - | - | - |
| **First-line ART regimen** | | | | | | |
| NNRTI-based | 7,870 | 20,345 | 104 | 511 (422-619) | 1.00 | 1.00 |
| PI-based | 664 | 2,172 | 6 | 276 (124-615) | 0.53 (0.23-1.21) | 0.66 (0.26-1.66) |
| Other ART | 26 | 71 | 2 | 2824 (706-11291) | 5.52 (1.36-22.39) | 10.52 (2.56-43.32) |
| **WHO clinical stage of HIV/AIDS at ART** | | | | | | |
| 1 | 3,277 | 9,377 | 42 | 448 (331-606) | 1.00 | 1.00 |
| 2 | 1,413 | 3,230 | 13 | 402 (234-693) | 0.91 (0.49-1.69) | 0.90 (0.48-1.67) |
| 3 | 2,023 | 5,821 | 30 | 515 (360-737) | 1.15 (0.72-1.83) | 1.08 (0.67-1.73) |
| 4 | 738 | 1,794 | 18 | 1003 (632-1592) | 2.25 (1.29-3.90) | 2.25 (1.29-3.93) |
| Missing | 1,109 | 2,366 | 9 | - | - | - |
| **CD4 cell count at ART start [cells/µl]** | | | | | | |
| < 50 | 1,954 | 5,572 | 31 | 556 (391-791) | 1.00 | - |
| 50-99 | 1,463 | 4,150 | 21 | 506 (330-776) | 0.91 (0.53-1.59) | - |
| 100-199 | 2,823 | 7,450 | 38 | 510 (371-701) | 0.92 (0.57-1.48) | - |
| ≥ 200 | 1,480 | 3,086 | 14 | 454 (269-763) | 0.83 (0.44-1.56) | - |
| Missing | 840 | 2,330 | 8 | - | - | - |
| **CD4 nadir [cells/µl]** | | | | | | |
| < 50 | 2,306 | 6,578 | 41 | 623 (459-846) | 1.00 | - |
| 50-99 | 1,735 | 4,957 | 22 | 444 (292-674) | 0.71 (0.43-1.20) | - |
| 100-199 | 3,253 | 8,545 | 38 | 445 (324-611) | 0.72 (0.46-1.11) | - |
| ≥ 200 | 1,250 | 2,469 | 11 | 445 (247-804) | 0.73 (0.37-1.42) | - |
| Missing | 16 | 38 | 0 | - | - | - |
| **Current CD4 cell count [cells/µl]** | | | | | | |
| < 100 | - | 939 | 7 | 746 (356-1564) | 1.00 | - |
| 100-199 | - | 2,882 | 13 | 451 (262-777) | 0.57 (0.23-1.44) | - |
| 200-349 | - | 6,657 | 37 | 556 (403-767) | 0.65 (0.29-1.47) | - |
| 350-499 | - | 5,932 | 24 | 405 (271-604) | 0.45 (0.19-1.06) | - |
| ≥ 500 | - | 6,052 | 31 | 512 (360-728) | 0.56 (0.24-1.32) | - |
| Missing | - | 126 | 0 | - | - | - |
| **Haemoglobin at ART start [g/dl]** | | | | | | |
| < 10.0 | 1,905 | 4,943 | 22 | 445 (293-676) | 1.00 | - |
| 10.0-11.9 | 2,920 | 7,711 | 38 | 493 (359-677) | 1.11 (0.66-1.88) | - |
| ≥ 12.0 | 3,019 | 7,890 | 42 | 532 (393-720) | 1.20 (0.72-2.01) | - |
| Missing | 716 | 2,044 | 10 | - | - | - |

* Restricted to 7,451 women with available WHO clinical stage of HIV/AIDS at ART start.

† Adjusted for age, calendar period of ART start, first-line ART regimen, and WHO clinical stage.

ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; ICC, invasive cervical cancer; IQR, interquartile range; HR, hazard ratio; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; WHO, World Health Organization.

**Supplementary Table S2: Hazard ratios for developing ICC in HIV-positive women who initiated ART.** Sensitivity analysis based on multiply imputed dataset.

| | Crude HR (95% CI) | Adjusted HR * (95% CI) |
|---|---|---|
| **Calendar period of ART start** | | |
| 04/2004-03/2005 | 1.00 | 1.00 |
| 04/2005-12/2008 | 0.81 (0.54-1.20) | 0.79 (0.53-1.18) |
| 01/2009-08/2011 | 0.37 (0.19-0.74) | 0.35 (0.18-0.71) |
| **Age at ART start** | | |
| 18-25 years | 1.00 | 1.00 |
| 26-35 years | 2.28 (0.99-5.26) | 2.15 (0.93-4.97) |
| 36-45 years | 2.89 (1.24-6.72) | 2.66 (1.14-6.21) |
| ≥ 46 years | 1.86 (0.72-4.79) | 1.71 (0.66-4.45) |
| **First-line ART regimen** | | |
| NNRTI-based | 1.00 | 1.00 |
| PI-based | 0.45 (0.20-1.1 | 0.50 (0.22-1.15) |
| Other ART | 6.75 (2.15-21.21) | 7.33 (2.31-23.27) |
| **WHO stage of HIV/AIDS at ART start** | | |
| 1 | 1.00 | 1.00 |
| 2 | 0.91 (0.53-1.57) | 0.89 (0.52-1.54) |
| 3 | 1.09 (0.72-1.65) | 1.01 (0.66-1.55) |
| 4 | 1.93 (1.17-3.19) | 1.87 (1.13-3.12) |
| **CD4 cell count at ART start [cells/µl]** | | |
| < 50 | 1.00 | - |
| 50-99 | 0.93 (0.56-1.56) | - |
| 100-199 | 1.00 (0.65-1.55) | - |
| ≥ 200 | 0.93 (0.53-1.61) | - |

* Adjusted for age, calendar period of ART start, first-line ART regimen, and WHO clinical stage of HIV/AIDS.

ART, antiretroviral therapy; CI, confidence interval; ICC, invasive cervical cancer; HR, hazard ratio; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; WHO, World Health Organization.