**Invasive cervical cancer in HIV-infected women: risk and survival relative to that of the general population in France.
Results from the FHDH-ANRS CO4 cohort**

**Short title**: Cervical cancer and HIV infection

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P Tattevin reports personal fees from Gilead Sciences, MSD, and Mylan for consultancies, and support from Janssen for travel/accommodations/meeting, outside the submitted work.

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**Abbreviations used :**

* ICC:Invasive cervical cancer
* **WLHIV : women living with HIV (WLHIV)**
* FHDH : French Hospital Database on HIV-Anrs CO4 cohort
* cART: combined Antiretroviral therapy
* SIR : standardized Incidence Ratio
* HPV : human papillomavirus
* ICD : International Classification of Diseases
* INSEE : National Institute of Statistics and Economic Studies
* RNIPP : Répertoire National d’Identification des Personnes Physiques
* CIN : cervical intraepithelial neoplasia
* IR : Incidence rate

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**KEY WORDS:** HIV/ AIDS infection, cervical cancer, Survival, cohort study

**ABSTRACT**

**Objectives: We examined trends for the incidence of** invasive cervical cancer (**ICC) and survival after ICC among women living with HIV (WLHIV) in France and compared them to those of the general population.**

**Methods:** Histologically-validated incident cases of ICC between 1992 and 2009 from the French Hospital Database on HIV (FHDH) were studied.Age-standardized incidence rates were estimated for FHDH and the general population in France for 1992-1996 (pre-cART), 1997-2000 (early cART), 2001-2004 (intermediate cART), and 2005-2009 (late cART). Age-standardized Incidence Ratios (SIR) were calculated. Five-year survival was compared to that of the general population for ICC diagnosed in 2005-2009 after standardization on age.

**Results:** Among 28,977 WLHIV, 60 incident ICCs were histologically validated. There was a non-significant decreasing trend for the incidence across the cART periods (p=0.07), from 60 to 36/100,000 PY. The risk of ICC was constantly significantly higher in WLHIV than in the general population; the SIR was 5.4 (95%CI, 3.0-8. 9) during the pre-cART period and 3.3 (95%CI, 2.2-4.7) in 2005-2009. Survival after ICC did not improve across periods (log-rank p=0.14), with overall estimated five-year survival of 78% (95%CI; 0.67-0.89%). Five-year survival was similar for WLHIV and the general population for women diagnosed with ICC in 2005-2009, after standardization (p=0.45).

**Conclusion:** ICC risk is still more than three-times higher in WLHIV than in the general population. Survival after ICC did not improve over time and was similar to that of the general population during the most recent period. Such results call for promoting the uptake of screening in WLHIV.

**INTRODUCTION**

Invasive cervical cancer (ICC) has been an AIDS-defining cancer since 1993 1 and is associated with human papillomavirus (HPV) infection. ICC is the fourth cause of cancer in women worldwide 2 and the leading cause of death in women living with HIV (WLHIV) in Sub-Saharan Africa 3. In high-income countries, WLHIV had a 5.8 fold higher risk of ICC relative to that of the general population in the early years of combined antiretroviral treatment (cART) 4. However, there are discrepant data concerning the temporal trends of incidence associated with the expansion of cART use 5,6. Studies published before 2010 7-10 showed no change in the incidence trends, whereas studies published since 2010 indicate a decreasing trend associated with cART use 11-13. Recently, a study from the WIHS cohort showed only a marginally higher risk of ICC in HIV-infected women than HIV-negative women in the US14. However, these results need to be confirmed, as previous studies were often underpowered due to the small number of ICC cases and lacked ICC validation, including in our previous published results 5,13. Moreover, the impact of HIV infection on survival after ICC has been less studied than for other cancers, due to the small number of ICC cases and deaths. Published data indicate a higher risk of mortality in HIV-infected women relative to uninfected women in the USA 15,16.

We took advantage of the large number of women followed in the French Hospital Database on HIV (FHDH-ANRS CO4 cohort) to examine the trends in the incidence of ICC over an 18-year period and the 5-year survival after ICC among HIV-infected women in France and compare them with those of the general population. At the time of the study, annual ICC screening was recommended for WLHIV and every three years for women between the ages of 25 and 65 in the general population for the diagnosis of cervical premalignant low to high grade squamous intraepithelial lesions.

**METHODS**

**Data sources and patients**

***Women living with HIV (WLHIV)***

The French Hospital Database on HIV FHDH-ANRS CO4 17 is an open nationwide hospital-based cohort created in 1989, in which clinical, therapeutic, and biological data on HIV-infected patients throughout France are prospectively recorded. The inclusion criteria for the FHDH are HIV1 or HIV2 infection and written informed consent. Clinical diagnoses, including cancer codes using the International Classification of Diseases, ninth revision (ICD-9) before 1997 and the tenth revision (ICD-10) thereafter, have been collected since 1989. The FHDH represented approximately 53% of the patients living with HIV in care in France in 2009.

From the 107,334 HIV-1 infected individuals followed in the French Hospital Database on HIV (FHDH-ANRS CO4) between 1992 and 2009, we included the women with at least one CD4 cell count available and a follow-up visit. Women from French overseas departments were not eligible for the study because data concerning the general population were not available (see below).

***General population in France***

Data for the French general population were obtained from the French Network of Population-Based Cancer Registries (FRANCIM), which included 21 registries covering French departments. Incidence data from 1992 to 2009 were obtained, thus covering the four periods of interest. Survival data for the general population were obtained for ICC diagnosed between 2005 and 2009 18 for whom the FRANCIM collected vital status data, according to a standardized procedure, via queries to the INSEE (National Institute of Statistics and Economic Studies-Répertoire National d’Identification des Personnes Physiques (RNIPP)), municipality of residence, or medical records 18.

***ICC ascertainment***

Only ICC that occurred after inclusion in FHDH (ie. incident ICC) were considered in this study. Therefore all prevalent ICC at the time of FHDH inclusion were excluded. All incident ICC cases reported in FHDH were validated based on the review of the original histology retrieved from the medical records of all ICC codes (ICD-9:180.x and ICD-10:C53.x). It was difficult to retrieve medical records prior to 2000 for women enrolled in the FHDH. Thus, the number of ICCs was corrected by applying the validation rate obtained in a given period to the non-retrieved cases of that period. Of note, these corrected numbers of ICC were used only for the estimations of incidence rates and standardized incidence ratio. We also verified the histology on a sample of WLHIV enrolled in the FHDH with ICD codes of cervical intraepithelial neoplasia (CIN) or *in situ* lesions.

**Statistical analyses**

Four calendar periods were considered: the pre- (1992–1996), early- (1997–2000), intermediate- (2001–2004), and late-cART periods (2005–2009). The choice of these periods of ICC diagnosis allowed studying the five-years survival following the diagnosis of ICC with the most updated data for both the HIV and general population. Incidence rates (IRs) were directly standardized using the age structure (by five-year age groups) of the female HIV population in the FHDH during the cART period (1997-2009), as reference, to allow comparisons across calendar periods, irrespective of the aging of the HIV cohort population. Trends in standardized ICC IRs across the four periods between 1992 and 2009 were tested using linear regression models. We compared the incidence of ICC in WLHIV to that of women from the general population in France by calculating the standardized incidence ratio (SIR) by dividing the corrected observed incident number of ICCs by the expected number obtained by multiplying patient-years at risk in each five-year age group of the HIV-infected population by the corresponding age-specific incidence rates in the general population. For the survival analysis, deaths from all causes were examined. The Kaplan-Meier method was used to estimate the five-year survival rates after ICC diagnosis between 1992 and 2009, stratified by diagnosis period and tested by the Log-rank test. We compared survival between WLHIV and the general population using the latest data available in FRANCIM for 2005 to 200918. Because the age and sex distributions differ between the HIV-infected and general populations, the five-year survival rate in the general population was standardized using the direct method, based on the age structure of HIV-infected women diagnosed with ICC. A t-test was used to compare five-year survival between WLHIV and women from the French general population.

SAS software version 9.4 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

**RESULTS**

Among the 29,009 WLHIV followed in the FHDH in mainland France between 1992 and 2009, with at least one follow-up visit and a CD4 cell count measurement, 32 had a prevalent diagnostic code of ICC at inclusion in the FHDH and were excluded (**Figure 1**), leaving 179 women with an incident code of ICC. Among them, medical records were not available for 56 women and ICC diagnosis was not confirmed following review of the histological report for 63 (49% of cases reviewed). Diagnoses validated to be something other than ICC were 32 (51%) cervical intraepithelial neoplasia (CIN)-3, nine (14%) CIN-2, six (10%) CIN-1, four (6%) *in situ* cancers, and 12 (19%) other diagnoses. The rate of adequate ICC diagnosis improved over time in the cohort; it was 37.5%, 41.4%, 53.3%, and 59.0% for the periods of 1992 to 1996, 1997 to 2000, 2001 to 2004, and 2005 to 2009, respectively. After applying the validation rate of a given period to the non-retrieved cases, the final number of corrected incident ICCs was 87: 14 from 1992 to 1996, 20 from 1997 to 2000, 22 from 2001 to 2004, and 31 from 2005 to 2009. Of note, none of the 38 ICD codes of CIN or *in situ* controlled by histology were found to be ICC.

 The characteristics of the 60 WLHIV diagnosed with a validated incident ICC are presented at the time of ICC diagnosis in **Table 1**. They had a median age of 39 years and had been mostly infected through heterosexual contacts more than eight years before. Fifteen percent of the women were from sub-Saharan countries and their proportion increased over the calendar periods. At ICC diagnosis, the median CD4 count was 301/mm3 and median nadir CD4 count 117/mm3. The proportion of women who had been on cART for more than six months was 41.6% from 1997 to 2000 and 87% from 2005 to 2009.

Age-standardized ICC incidence rates (IR) and SIR are presented in (**Table 2**). The incidence of ICC was constantly higher in WLHIV than in the general population. In WLHIV, there was a non-significant decreasing trend for the incidence across cART periods (p = 0.07), from 60 to 36/100,000 PY in the last cART period. The decreasing trend of the incidence for the general population was highly significant: 13.9 to 10.7/100,000 PY (p < 0.0001). The relative incidence reduction between 1997-2000 and 2005-2009 obtained by dividing the incidence rate difference by the incidence rate in 1997-2000 was 39.3% in WLHIV and 18.5% in the general population (p=0.26). The SIRs confirmed the significant higher risk of cervical cancer among WLHIV relative to that of the general population in all the calendar periods. In 2005-2009, the SIR was 3.3 .

Among the 60 WLHIV diagnosed with ICC, 13 died during follow-up of whom 10 from ICC. Survival after ICC did not improve over time (Log-Rank; p = 0.11) (**Figure 2**). The five-year survival rate was 77% (95%CI; 64-86%) for WLHIV *diagnosed with ICC between 1992-2009*. The age-standardized five-year survival rate for women of the general population diagnosed from 2005 to 2009 was 74% (95%CI; 72-76%) after standardization for the age of WLHIV diagnosed with ICC. This survival rate did not significantly differ from the 66% (95%CI; 41-82%) survival rate observed for WLHIV *diagnosed with ICC between the 2005-2009* (p = 0.45).

**DISCUSSION**

Our results from a large cohort of HIV-infected patients, the FHDH-ANRS CO4 study, show a decreasing trend for the incidence of ICC since the advent of cART, which did not reach significance. However, in the most recent period, the risk of ICC was still more than three-times higher for HIV-infected women than for the general population. Survival after ICC of WLHIV did not improve over time and was similar to that of women from the general population in the most recent period.

***Limitations and strengths***

Strength of our study was the ascertainment of the ICC diagnosis by the review of histopathology reports. We anticipated that the diagnosis of CIN could have been miscoded in ICC in FHDH. Thus, each case was reviewed and validated with original histological data from medical charts. As expected, approximately half of the cases were misclassified as CIN. Similar rates of misclassification were reported in NA-ACCORD study where only 56% of the ICCs identified were validated 19. Not having performed this validation step would have led to an overestimation of the incidence of ICC. Such overestimations have probably affected many previous studies of ICC that did not rigorously confirm the ICC diagnosis20,21.

Underreporting of ICC in the FHDH may also be a limitation, as FHDH centers are not specifically involved in oncological care, but mostly in that for HIV. However when we estimated the completeness of notification of various cancers in the FHDH in a previous study using a capture–recapture method, the completeness of the ICC diagnosis was estimated to be 86% 22. It was the highest completeness observed for AIDS-defining (LNH and KS) and non-AIDS-defining cancers. There is no particular reason why underreporting would have distinctly affected the different calendar periods. Thus, we believe that even if underreporting may have slightly underestimated the incidence rates it is unlikely to have affected the incidence trends overtime.

Despite the importance of person-time in our study, lack of power was also a limitation which may have led to non-statistically significant results in the incidence temporal trends and survival analyses. This pleads for caution in the interpretation of the results and the need of larger studies to confirm these results. Other limits are the lack of ICC stage and treatment and of information on history of screening that are not available in the FHDH.

***Incidence and SIR***

Several studies have assessed the impact of HIV infection on cervical cancer, mostly showing a higher risk than that in the general population. Our data confirm the significant over-risk in all the studied periods in WLHIV from 5.4 to 3.3 between the periods of 1992 to 1996 and 2005 to 2009. Our data show a trend towards a decrease in the incidence rates although it did not reach significance (p=0.07) likely due to insufficient power. Our results are remarkably consistent with those observed in other contexts in high-resource countries. In Grulich et al. meta-analysis 4 from cases occurring before 2002, the SIR was 5.82 (CI95%; 2.98-11.3) which is close to the SIR observed in our study. Data from three American studies covering a more recent period showed a roughly three-fold higher risk of ICC among WLHIV 14,23. The SIR was 3.24 (95%CI; 2.94-3.56) in a large registry-linkage study of cases from 1996 to 2012 23 and 3.31 (95%CI; 0.90-8.47) with borderline significance, due to the small number of ICC (N = 4), in the American WIHS study of cases before 2015 14. It was 4.1 (95%CI; 2.3-6.6) in the NA-ACCORD study 19 of cases from 1996 to 2010. The calendar trend was only analyzed in a study by Hernandez-Ramirez et al.,23 whichfound after multivariate adjustment that the SIR appeared to decrease over time, but that the trend was not statistically significant (p = 0.10). The decreasing trend of ICC incidence may be explained by better screening of ICC over the calendar periods and treatment of pre-cancer stages or by the effect of cART on lesions, although results from the literature are inconsistent 6,24. HPV vaccination is unlikely to be an explanation, given the age of the WLHIV cohort and the very low coverage of this vaccination in France. 25

***Survival***

Few studies have considered survival after ICC in WLHIV, given the relatively small number of ICC cases and deaths. In our cohort, the five-year survival rate was 74%, which is close to that observed by others in the USA26, and much better than that observed in African 3,27, where the three-year survival was estimated to be 35% in WLHIV3. We observed no improvement in survival across the calendar periods among WLHIV, nor did we observe differences in survival in the more recent period relative to that of the general population. In the literature, comparisons with the general population were mostly estimated through HIV/AIDS and cancer registries although cancer registries in most countries do not document HIV infection. ln the USA, a study from six states estimated a non-significant 1.4-fold higher risk of cancer-specific mortality 16, in contrast to a significant six-fold higher risk observed in Florida 28 among WLHIV over that of uninfected women and previous results 15 estimating a significant 1.8-fold risk among women with AIDS relative to women without AIDS. After adjusting for cancer-stages, a Brazilian study has found that the HR was two-fold higher for overall mortality and four-fold for cancer specific mortality. 29

Late stage presentations are a concern for cancer survival and ICC outcomes have been shown to be related to access to care in the USA 30. Cancer-stages could unfortunately not be examined in our study because this information was not available in the FHDH. The lack of a difference in ICC survival according to HIV status, shown by our results, might indicate that the diagnosis of ICC in France is made at the same cancer-stage for both populations. This however needs to be confirmed and to be interpreted together with the result of a study performed on a representative sample of WLHIV followed in French hospitals showing that the uptake of cervical screening was slightly better for WLHIV than in the general population of France (88.2% *vs* 82.8%), but was suboptimal given the specific recommendations for WLHIV at the time of the study that called for more frequent screening in WLHIV than for uninfected women 31. Dryden-Peterson *et al*. 3 reported that the excess risk of death between WLHIV and uninfected women was greater for early stages for women in Botswana, which may reflect a lesser access to treatment for these women. However, the situation is likely different in France as in industrialized countries of and would need to be studied in more detailed.

***CONCLUSIONS***

Overall, our study provides encouraging results, showing a decreasing trend of ICC incidence in WLHIV over time and a probability of survival after diagnosis similar to that of uninfected women. However, the risk of developing ICC is still three-times higher than in the general population and calls for continuing efforts on improving the uptake of screening and of HPV vaccination in WLHIV.

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**Members of the FHDH-ANRS C04 Cohort** are listed at: http://www.ccde.fr/main.php?main\_file=fl-1171464013-677.html

**AUTHORS’ CONTRIBUTIONS**

SG and DC designed the study.

MH performed the statistical analyses.

SG, MH, and AB and DC interpreted the data and drafted the manuscript.

All the authors read and critically commented on the paper.

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**FIGURE LEGENDS**

**Figure 1.** Flow chart

**Figure 2**. Survival following invasive cervical cancer in WLHIV by calendar period

**Figure 1.** Flow chart

**33,015 WLHIV** enrolled in the FHDH among HIV-1 infected adults in mainland France

and followed between 1992-2009

**29,009** with at least one follow-up visit

and one CD4 cell count measured between 1992 and 2009

ICD codes of ICC\* n = **211**

**ICC analysis**

**28,977** women

Incident ICD codes of ICC\* **n = 179**

**60** **validated incident ICC**

with histology in the medical records

N per period2: 9/12/16/23

**32** prevalent ICD codes of ICC at FHDH inclusion

- Medical records not found (n = 56)

- ICC diagnosis not confirmed through histology review (n = 63) 1

After correction based on validation rate

**87** **corrected** **incident ICC** usedfor incidence rates estimations

N per period2: 14/20/22/31

|  |
| --- |
| \* International Classification of Disease (ICD) codes for ICC used were ICD9:180.x and ICD10:C53.x ICC: Invasive Cervical Cancer1 Diagnoses not confirmed through histology review were: cancer *in situ* (n = 4), CIN-3 (n = 32), CIN-2 (n =9 ), CIN-1 (n = 6), unspecified CIN, or other diagnoses (n = 12)2 Periods: 1992-1996/ 1997-2000/ 2001-2004/ 2005-2009 |

**Figure 2**. Survival following invasive cervical cancer in WLHIV by calendar period

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**Table 1**. Characteristics of WLHIV at invasive cervical cancer diagnosis in the FHDH between 1992 and 2009.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  **All periods (n = 60)** | **1992-1996****(n = 9)** | **1997-2000****(n = 12)** | **2001-2004****(n = 16)** | **2005-2009****(n = 23)** |
| **Age at diagnosis** | 39 (36-46) | 31 (29-36) | 27 (35-48) | 42 (37-48) | 42 (38-46) |
| **Transmission route** |  |  |  |  |  |
| Heterosexual | 36 (60.0) | 2 (22.2) | 6 (50.0) | 12 (75.0) | 16 (69.6) |
| IV Drug user | 20 (33.3) | 7 (77.8) | 5 (41.7) | 3 (18.8) | 5 (21.7) |
| Other | 4 (6.7) |  | 1 (8.3) | 1 (6.2) | 2 (8.7) |
|  |  |  |  |  |  |
| **Geographic origin** |  |  |  |  |  |
| Sub-Saharan  | 9 (15.0) | 0 | 1 (8.3) | 3 (18.8) | 5 (21.7) |
| Non-sub-Saharan  | 51 (85.0) | 9 (100) | 11 (91.7) | 13 (81.2) | 18 (78.3) |
| **Prior AIDS-defining opportunistic infections**  | 16 (26.7) | 2 (22.2) | 3 (25.0) | 2 (12.5) | 9 (39.1) |
| **Known duration of HIV infection** (years) | 8.5 (5.0-15.3) | 7.0 (3.0-8.2) | 8.5 (5.4-13.5) | 7.7 (3.8-12.1) | 15.5 (6.0-18.0) |
|  |  |  |  |  |  |
| **HIV RNA copies/mL at diagnosis** | 499 (499-9120) | - | 499 (499-120000) | 499 (499-2790) | 499 (49-10380) |
| **HIV RNA ≤ 500 copies/mL at diagnosis\*** | 33 (67.3) | - | 6 (50.0) | 11(68.7) | 16 (69.6) |
| **CD4 at diagnosis cells/mm3** | 301 (110-502) | 288 (110-500) | 342 (273-496) | 359 (145-549) | 226 (90-502) |
| **Nadir CD4 cells/mm3** | 117 (50-267) | 200 (37-402) | 177 (98-270) | 146 (79-288) | 115 (23-173) |
| **Antiretroviral Treatment\*\*** |  |  |  |  |  |
| Naïve  | 10 (16.7) | 5 (55.6) | 2 (16.7) | 2 (12.5) | 1 (4.3) |
| ARV, not cART | 10 (16.7) | 4 (44.4) | 3 (25.0) | 2 (12.5) | 1 (4.3) |
| cART for less than 6 months  | 6 (10.0) |  | 2 (16.7) | 3 (18.8) | 1 (4.3) |
| cART for more than 6 months | 34 (56.6) |  | 5 (41.6) | 9 (56.2) | 20 (87.0) |

Data are presented as counts (proportions) and medians (Inter-Quartile Range).

Abbreviations: cART - combined antiretroviral therapy, ARV - antiretroviral drugs

\*HIV RNA data were available for 49 women (81.6%)

\*\*cART is defined as boosted protease inhibitor monotherapy, irrespective of the protease inhibitor; dual therapy with two boosted protease inhibitors or one boosted protease inhibitor plus one non-nucleoside reverse transcriptase inhibitor; or at least one boosted protease inhibitor or with an integrase inhibitor and/or an anti-CCR5 drug; or a combination of 3 or more drugs.

**Table 2.** Incidence rate of ICC standardized for age (per 100,000 person-years) and standardized incidence ratio by calendar periods

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **1992-1996** | **1997-2000** | **2001-2004** | **2005-2009** | *P for trend across 4 periods* | *P for trend across post-cART periods* |
| **Number of person-years in WLHIV** | 30223 | 40383 | 52617 | 80656 |  |  |
| **IR in WLHIV [95%CI]** | 51.1 [18.3-83.8] | 59.8 [32.6-87.1] | 41.8 [23.9-59.7] | 36.3 [23.3-49.3] | 0.10 | **0.075** |
| **IR in General population [95%CI]** | 13.9 [13.1-14.7] | 13.2 [12.3-14.0] | 12.0 [11.2-12.8] | 10.7 [10.1-11.3] | < **0.0001** | < 0.0001  |
| **Observed/Expected n****SIR [95%CI]** | 14.6/2.7 5.4 [3.0- 8.9] | 19.9 / 4.5 4.4 [2.7 - 6.8] | 21.3 / 6.3 3.4 [2.1- 5.1] | 30.7/ 9.36 3.3 [2.2 - 4.7] | 0.086 | 0.354 |

IR: Incidence rate of ICC standardized for age (per 100,000 person-years)

[95%CI] 95% confidence interval

SIR: Standardized incidence Ratio