Pancreatic cancer in people with HIV: an emerging concern?

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Introduction

Life expectancy of people with HIV (PWH) with appropriate care with antiretroviral drug therapy and cardiovascular prevention continues to increase and is virtually indistinguishable from people without HIV. Consequently, cancer is becoming one the leading causes of death in PWH, surpassing opportunistic infections and cardiovascular diseases. Pancreatic cancer is one the one leading causes of oncologic death in high-income countries. Furthermore, pancreatic neoplasms are on the rise, although it is still unclear why. Data on pancreatic cancer in PWH are scarce but tend to show that PWH might have a higher incidence than expected in the general population and a tendency towards more aggressive tumors. Classical risk factors for pancreatic cancer such as smoking, and alcohol consumption might be more prevalent and more potent in PWH. Pancreatic cancer then appears as a particular concern for physicians involved in the long-term care of PWH.

Aim
We aimed to estimate the incidence of pancreatic cancer in a cohort of PWH and to determinate the risks factors for pancreatic cancer in PWH.

Materials and Methods:

A case-control study was designed using data extracted from the COREVIH Ile-de-France-Est database.
We defined a case as a person with a diagnosis of seropositivity for HIV (proven with at least two positive tests) and a definitive histological proof of pancreatic carcinoma or neuroendocrine tumor. Each case was matched to four controls (PWH and no pancreatic cancer) in the database, matched on age, gender and duration of HIV-infection.
We collected data on patient demographics (age, sex, past history of pancreatic disease, diabetes, tobacco or alcohol habitus), HIV history (CDC stage, mode of transmission, past history of opportunistic infections, treatment history (received drugs and duration), and immuno-virologic status (CD4 at time of cancer diagnosis, nadir CD4, CD4 in the 12 months before cancer diagnosis, viral load at cancer diagnosis, zenith viral load, duration of undetectable status before cancer).

Statistical analysis:
Categorical variables are presented as "Absolute number (percentage)" and quantitative variable as "Mean (standard deviation)". Univariate analyses were adjusted for multiple-comparisons and conducted using Spearman Rank Correlation Coefficient, ANOVA, and Chi^2 tests when appropriate. Statistical significance was defined for a p-value inferior to 0.05 after adjustment for multiple comparison.
The risk factors for pancreatic cancer analyzed were: past history of diabetes, CD4 nadir, duration of each antiretroviral drug individually

Results:
From 2009 to 2020, in six hospitals in the Paris region, twenty-five cases were identified from the database, and 24 were included in the case control study **with 96 controls**.
Incidence for pancreatic cancer was estimated at 28 cases (95% CI:[5-108]) per 100,000 person-years.
Demographics and HIV parameters are summarized in Table 1 and figure 1. Most cases were male (88%; n=22), aged 57 years in median (IQR [51-58]) at the time of cancer diagnosis.
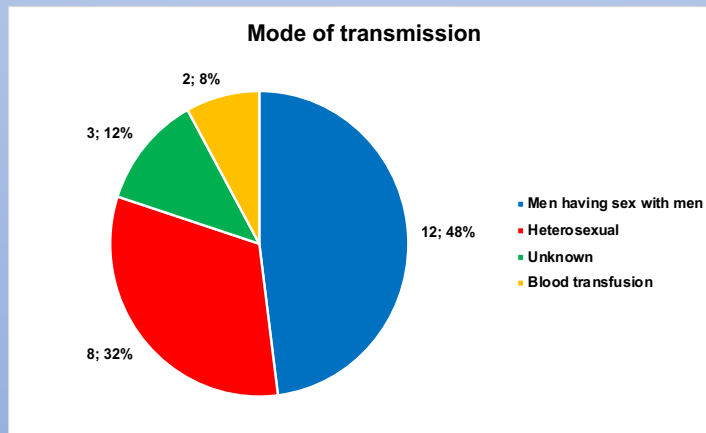Although nadir CD4 was relatively low (median 208/mm3 IQR[102-387]), at the time of cancer diagnosis, median CD4: 641/mm3 IQR [352-840]). Cancer was diagnosed at an advanced stage with 48% (n=12) with metastasis on diagnosis. Death rate among cases was 91% (n=18) and a median time to death of 11 months [IQR 1-21] Figure 2. Cancer types are summarized figure 3.
No statistically significant risk factors for PC were found in the case-control analysis but there might be a trend toward an increased risk with the duration of some antiretroviral drugs. Table 2.
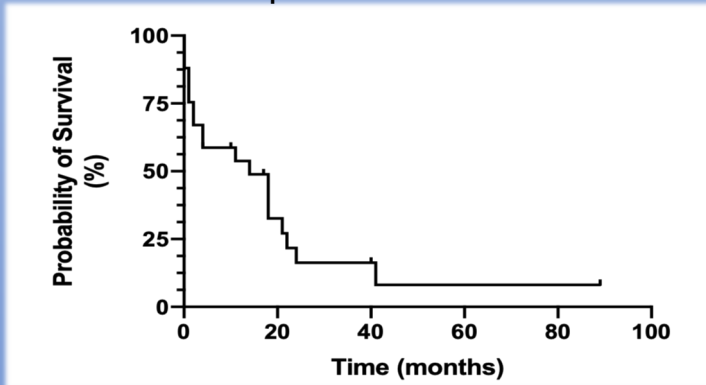
Table 1. Demographics, HIV characteristics and cancer outcome

	n or median (% or IQR)
Age in years at cancer diagnosis	57 (51-68)
HIV duration of evolution	17 (3-22)
Sex (male)	22 (88)
Alcohol consumption (current or past)	2 (10)
Tobacco consupption (current or past)	8 (38)
Mode of HIV transmission	
MSM	12 (48)
Heterosexual	8 (32)
Blood transfusion	2 (8)
Unknown	3 (12)
CD4 nadir	208 (102-387)
Opportunist infection in the past	4 (33)
Highest viral load (log)	10 (5-12)
Duration of indetectability before cancer (years)	7 (5-7)
CD4 at the time of cancer	641,5 (352-840)
Metastasis at diagnosis of cancer	12 (48)
ART received:	
Nucleoside inhibitors	21 (84)
Protease inhibitors	16 (64)
Integrase inhibitors	14 (56)
Non nucleoside inhibitors	10 (40)
Outcome	
Death	19 (91)
Survival (duration in months)	11 (1-21)

Figure 1. HIV mode of transmission

Mode of transmission
- 12; 48% — Men having sex with men
- 8; 32% — Heterosexual
- 3; 12% — Unknown
- 2; 8% — Blood transfusion

Figure 2. Kaplan Meier survival distribution of pancreatic cancer

Figure 3. Cancer type distribution

Cancer type
- 14; 54% — Adenocarcinoma
- 9; 34% — Non neuroendocrine undetermined
- 1; 4% — Cholangiocarcinoma
- 1; 4% — Neuroendocrine
- 1; 4% — Undifferenciated
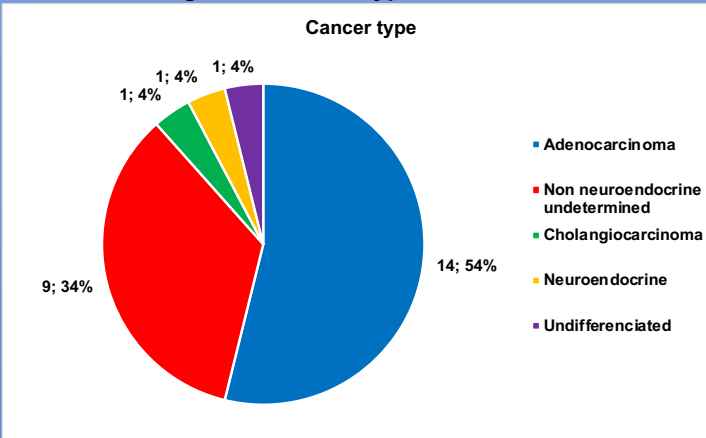
Table 2. Case-control study

Parameters	Cases N=24	Controls N=96	p-value
Gender, no (%)			1.00
Male	21 (87.5)	84 (87.5)	
Female	3 (12.5)	12 (12.5)	
Age in years at cancer diagnosis, median (IQR)	60 (54-68)	58 (54-67)	0.67
Age at HIV diagnosis in years, median (IQR)	39 (34-53)	39 (34-53)	0.91
CD4 at cancer diagnosis, median (IQR)	555 (344-738)	585 (400-743)	0.74
Nadir CD4, median (IQR)	222 (102-365)	213 (96-316)	0.75
Highest viral load (cp/ml), median (IQR)	10^5(21578-264365)	62372 (3857-306436)	0.45

Duration in years of ART, median (IQR):

	Cases N=24	Controls N=96	p-value
Zidovudine	0 (0-32)	0 (0-40)	0.91
Efavirenz	0 (0-13)	0 (0-26)	0.68
Nevirapine	0 (0-1)	0 (0-0)	0.76
Stavudine	0 (0-2)	0 (0-9)	0.87
Abacavir	4 (0-71)	0 (0-32)	0.11
Lamivudine	18 (2-75)	2 (0-95)	0.26
Tenofovir	42 (14-98)	13 (0-97)	0.12
Emtricitabine	30 (6-83)	3 (0-76)	0.08
Indinavir	0 (0-0)	0 (0-0)	0.73
Darunavir	0 (0-2)	0 (0-0)	0.48
Atazanavir	0 (0-36)	0 (0-0)	0.16
Saquinavir	0 (0-0)	0 (0-0)	0.78

Pancreatic cancer in the general population (for reference):

- In France, median age at diagnosis of pancreatic cancer is 70 years in men and 74 years in women
- 9% survival rate at 5 years in North American registers
- 52% metastasis on diagnosis

Bibliography:
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Conclusions:
Although pancreatic cancer remains a rare occurrence in PWH, it seems to appear at a younger age and to be aggressive.
We could not identify risk factors for pancreatic cancer in this case-control study in PWH but our analysis lacked power.
A larger study is needed to confirm these trends and identify risk factors for pancreatic cancer in patients PWH.