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Incidence trends of Kaposi's Sarcoma in the HAART era and comparison of different HAART Regimens. Results from the French Hospital Database on HIV.

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ABSTRACT

Background: Evidence indicates that protease inhibitors (PI) might have a specific anti-Kaposi's sarcoma (KS) activity. This suggests that a PI-containing HAART regimen may be more effective in preventing KS than other HAART regimens. We studied the incidence rates of KS in 4 calendar periods of time characterized by different ART availability and studied the factors associated with KS.

Methods: Patients were selected from the French Hospital Database on HIV, a large prospective hospital cohort. Hazards of KS was estimated by Cox proportional hazards models adjusting for age, nadir of CD4, HIV exposure category, prior diagnosis of AIDS, initiation of a mono, and dual or HAART regimens. Several HAART regimens were distinguished according to whether they contained PI, non-nucleoside analogue (NNRTI), both, or only NRTI. All treatment variables were included as time dependent variables.

Results: A total of 1634 patients with KS were identified from the 54,999 patients included in the study (182,752 person-years of follow-up). The incidence rate of KS decrease over time from 32 of 1000 person-years in 1993-1994 to 3 of 1000 person-years after 1999. In the most recent period, KS occurred at higher median CD4 cells counts (134 vs 24 cells/mm³, $p < 0.0001$). In the multivariate analysis, age at entry into the database, nadir of CD4 cells count, previous AIDS diagnosis, homosexual transmission were associated with an increased risk of KS. Prescription of HAART containing PI was associated with a significant decreased risk of KS (0.82; CI 0.72 to 0.93). HAART containing NNRTI was associated with a similar reduced risk although non significant (0.83; 0.67 to 1.03). When restricting the analysis to homosexual patients the reduction associated with the use of HAART with PI and HAART with NNRTI was similar (0.68 and 0.71) and both significant. Use of HAART with NRTI was associated with a reduced risk of KS (0.83 and 0.88) in both populations although not significant.

Conclusions: There has been a dramatic reduction of incidence of KS since the introduction of HAART. Similar reduction of KS incidence was observed in patients taking HAART including PI and HAART including NNRTI indicating that PI and NNRTI might be equally effective in preventing KS. The same tendencies were observed with NRTI-containing HAART, but larger treated-populations are required to confirm these results.

BACKGROUND

- Epidemiology : since the Haart era, there has been a marked decline in the incidence of Kaposi Sarcoma
- Experimental data : evidences indicates that Protease Inhibitor (PI) regimen might have a proper anti-KS activity independently from the immune restoration. This is understood to be related to the anti-angiogenic effects of protease inhibitors. Thus, by direct and/or indirect activities, protease inhibitors can simultaneously block several pathways involved in tumor growth, invasion, and metastasis.
- => This suggests that antiretroviral treatment (ART) including PI might have a higher impact on KS than other therapeutic regimen

OBJECTIVES

- To study the impact of HAART on KS incidence
- To study the factors associated with occurrence of KS
- To compare different Haart regimen (containing PI, NNRTI, or only NRTI)

PATIENTS

The FHDH database

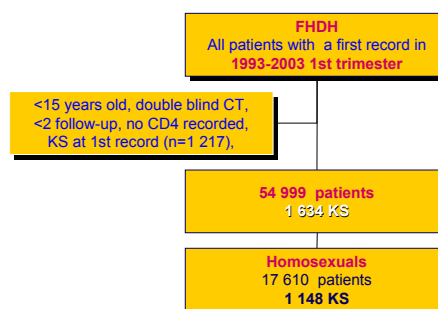
- French Hospital Database on HIV (FHDH) Set-up in 1989. 62 hospitals.
- Inclusion criteria:
 - confirmed HIV-1 or HIV-2 infection
 - to be followed in an hospital
 - to have signed an informed consent
- Data are collected prospectively by trained research assistants
 - DMI2 software
 - From medical records on standardised f/up form
- > 41 000 patients were followed in 2003

Statistical methods :

- 4 calendar periods characterized by different ARV availability were distinguished :
 - 1993- 1994 (monotherapy)
 - 1995-1996 1st trimester (dual therapy)
 - 1996 2nd trimester-1998 (mostly Haart including PI)
 - 1999-2003 1st trimester (various Haart but mostly including PI or NNRTI)
- Follow-up was censored on 1st April 2003
- Multivariate analyzes:
 - Cox proportional hazards models
 - Event: first occurrence of KS (not recurrences)
 - Adjusted for :
 - age at entry in FHDH, nadir of CD4 cells counts, sex and HIV exposure category (homosexual men, women versus other), prior Aids diagnosis, initiation of a monotherapy, dual or Haart regimens, notion of sub-Saharan African origin.
 - Time dependent variables : occurrence of a previous AIDS-defining illness, initiation of treatments (mono, dual, Haart including PI, Haart including NNRTI, Haart including only NRTI, Haart including PI and NNRTI)

- Antiretroviral Treatments :
 - Intent-to-continue treatment principle
 - Haart definition: a combination of more than 3 molecules
 - Modeled as time dependent variables
- Sub-analyzes were conducted in homosexual patients only

Figure1: Patients Selection



RESULTS

- Among the 54 999 patients (182 756 person-years of follow-up), a total of 1634 new KS were observed.

Table 1 : Description of the population

| | | Without KS 53 365 pts | With incident KS 1 634 pts | p |
|---------------------------------------|--------------------------|--------------------------|-------------------------------|--------|
| Gender (%) | Men | 70.1 | 95.2 | 0.0001 |
| Transmission Group(%) | Homosexual | 30.9 | 70.2 | |
| | Men other than msm | 39.2 | 25.0 | |
| | Women | 29.9 | 4.8 | |
| Pre-existing AIDS at baseline (%) | | 7.9 | 13.9 | 0.0001 |
| KS defining AIDS (%) | | na | 73.0 | |
| Sub-saharan origin (%) | | 9.0 | 3.5 | 0.0001 |
| Age at entry in FHDH | median (IQR) | 34.4 (29.6-41.0) | 37.0 (31.5-44.7) | 0.0001 |
| Nadir CD4 count cells/mm ³ | median (IQR) | 202 (69-349) | 40 (11-150) | 0.0001 |
| TREATMENTS First HAART regimen (%) | No haart | 34.8 | 38.4 | |
| | Haart including PI | 44.4 | 52.0 | |
| | Haart including NNRTI | 12.7 | 4.5 | |
| | Haart with only NRTI | 6.6 | 4.1 | |
| | Haart including PI+NNRTI | 1.5 | 1.0 | 0.0001 |

Figure 2: Incidence rates of KS in homosexual men and other HIV transmission group

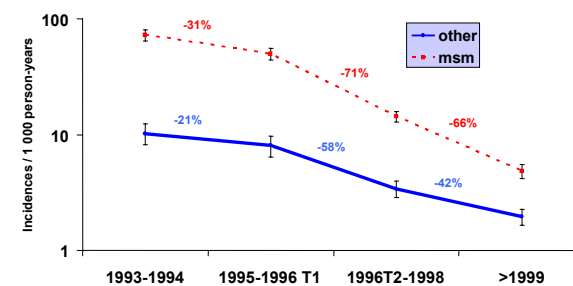


Table 3: Risk of developing KS. Multivariate analyzes in all patients (n=54 944 patients) and in homosexual patients (n=17 610)

| | All patients | | | Homosexual patients | | |
|--|--------------|-------------|--------|---------------------|------------|--------|
| | HR | 95% CI | p | HR | 95% CI | p |
| Men other than homosexual | 1 | | | | | |
| Homosexual men | 3.91 | 3.48 - 4.39 | <.0001 | | | |
| Women | 0.32 | 0.25 - 0.41 | <.0001 | | | |
| Age (/10 year increase) | 1.19 | 1.13 - 1.25 | <.0001 | 1.13 | 1.1 - 1.2 | <.0001 |
| Sub-saharan origin | 1.28 | 0.97 - 1.69 | 0.08 | | | |
| Nadir CD4 count (cells/mm ³) | | | | | | |
| >200 | 1 | | | 1 | | |
| 101-200 | 1.62 | 1.36 - 1.94 | <.0001 | 1.62 | 1.3 - 1.99 | <.0001 |
| 51-100 | 2.84 | 2.37 - 3.42 | <.0001 | 2.79 | 2.2 - 3.48 | <.0001 |
| <50 | 4.65 | 4.01 - 5.39 | <.0001 | 4.85 | 4.1 - 5.77 | <.0001 |
| AIDS non KS* | 1.43 | 1.27 - 1.61 | <.0001 | 1.35 | 1.2 - 1.56 | <.0001 |
| Monotherapy* | 2.19 | 1.96 - 2.45 | <.0001 | 2.22 | 1.9 - 2.54 | <.0001 |
| Dual therapy* | 1.04 | 0.93 - 1.17 | 0.50 | 1.02 | 0.9 - 1.17 | 0.74 |
| Haart including PI* | 0.82 | 0.72 - 0.93 | 0.002 | 0.68 | 0.6 - 0.80 | <.0001 |
| Haart including NNRTI* | 0.83 | 0.67 - 1.03 | 0.09 | 0.71 | 0.5 - 0.95 | 0.02 |
| Haart including only NRTI* | 0.83 | 0.63 - 1.11 | 0.21 | 0.88 | 0.6 - 1.25 | 0.47 |
| Haart including NNRTI and PI* | 0.92 | 0.67 - 1.26 | 0.58 | 0.97 | 0.7 - 1.43 | 0.86 |

*time dependent variables

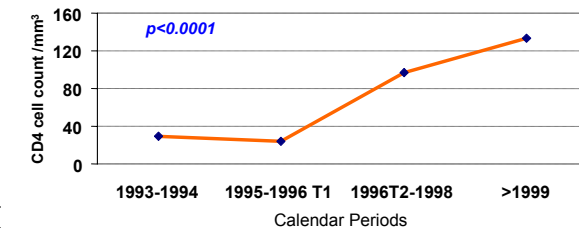
CONCLUSION

- There has been an important decrease in the incidence rate of KS since the introduction of potent therapy (1996).
- To date the incidence is closed to 2.9/1000 person-years (about 80 KS/year in the FHDH). It was 30/1000 before 1995 (>300 KS/year).
- The decline in the incidence is more pronounced since 1999 and among homosexuals.
- KS occurred at higher CD4 cell count in the recent periods.
- Similar reduction of KS incidence was observed in patients taking HAART including PI and HAART including NNRTI suggesting that PI and NNRTI might be equally effective in preventing KS.
- The same tendencies were observed with NRTI-containing HAART, but larger treated-populations are required to confirm these results.

Table 2: Incidence rates of KS (all patients N=54 999 patients)

| Calendar Periods | KS frequency | PY of follow-up | Incidence rate /1000 PYFU (95%CI) |
|------------------|--------------|-----------------|-----------------------------------|
| 1993-1994 | 439 | 13 783 | 31.9 (28.9-34.8) |
| 1995-1996T1 | 378 | 17 255 | 21.9 (19.7-24.1) |
| 1996T2-1998 | 476 | 66 519 | 7.2 (6.5-7.8) |
| >1999 | 341 | 116 237 | 2.9 (2.6-3.2) |

Figure 3: Median CD4 cell count at KS over the 4 calendar periods (N=1634)



- Prescription of HAART containing PI was associated with a significant decreased risk of KS (0.82; CI95% 0.72 to 0.93). (Table 3)
- HAART containing NNRTI was associated with a similar reduced risk although non significant (0.83; CI95% 0.67 to 1.03).
- When restricting the analysis to homosexual patients (n=17 610 patients), the reduction associated with the use of HAART with PI and HAART with NNRTI was similar to those obtain in the whole population (0.68; CI95% 0.58 to 0.80 and 0.71; CI95% 0.54 to 0.95) and both significant.
- Use of HAART including only NRTI was associated with a reduced risk of KS (0.83; CI95% 0.63 to 1.11) and 0.88 (CI95% 0.62-1.25) in both populations although not significant.