Relationships between markers of immunodeficiency and non AIDS related causes of death in cART era

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Introduction

In the cART era, epidemiological studies have shown

- ➔ significant reduction of death rates
- ➔ more than half of deaths are non AIDS-related
- ➔ association between latest markers of HIV infection and specific non AIDS deaths (end stage liver diseases, malignancies)

Emerging questions

- ➔ Is nadir CD4 count stronger determinant than latest values?
- ➔ Is time spent under 350 cellsx10^6/l a valuable prognosis factor?
- ➔ If a relationship exists with any marker of immunodeficiency, is there a gradient?

Objectives

To assess adjusted relationships between markers of immunodeficiency and specific causes of death

3 models were compared using

1 ➔ **Latest CD4 count** (usual approach, to be compared to others methods)

2 ➔ **Nadir CD4 cell count** (before cART and during follow-up)

3 ➔ **Time spent under 350 cellsx10^6/l**

Methods (1)

Population study

- **CASCADE Collaboration** : 23 seroconverters cohorts from Europe, Australia, Canada http://www.ctu.mrc.ac.uk/cascade
- Patients with available follow-up > 1996 (cART era), aged 16 years and more
- Availability of biological markers

Causes of death

- Standardized according to « Coding of Death in HIV (CoDe)» http://www.cphiv.dk

Methods (2)

Context of competing risks

- Modelling of **cause specific hazards ratios** based on Cox proportional hazards modelling
- Baseline time : time from seroconversion to death or censoring date

Variables

- Biological markers and time under 350 cellsx10^6/l: time varying covariates
- Adjustment for : age at seroconversion date, sex, mode of HIV transmission, Hepatitis C serostatus and first line cART treatment (PI-regimen, other cART vs no cART)

Results (1)

Table 1: Sociodemographic and clinical characteristics of patients

Sociodemographic and clinical characteristics	Patients N=9 858	
	Median/N	IQR/%
Age at seroconversion	**30**	25.2-36.6
Male	7 543	**76.5**
Modes of HIV transmission		
Sex between men	5 358	**54.4**
Injecting drug use	1 412	**14.3**
Sex between men and women	2595	**26.3**
Other	493	**5.0**
Hepatitis C co-infection†	1 708	**21.9**
cART during folllow-up	6 530	**66.2**
AIDS stage C during follow-up	1 280	**13.0**
Death	597	**6.1**

† Information was available for 7793 (79%) included patients.

N, Number; IQR, Interquartile range.

Overall 9 858 patients were followed for a median of 8 years after seroconversion
2/3 initiated cART during follow-up

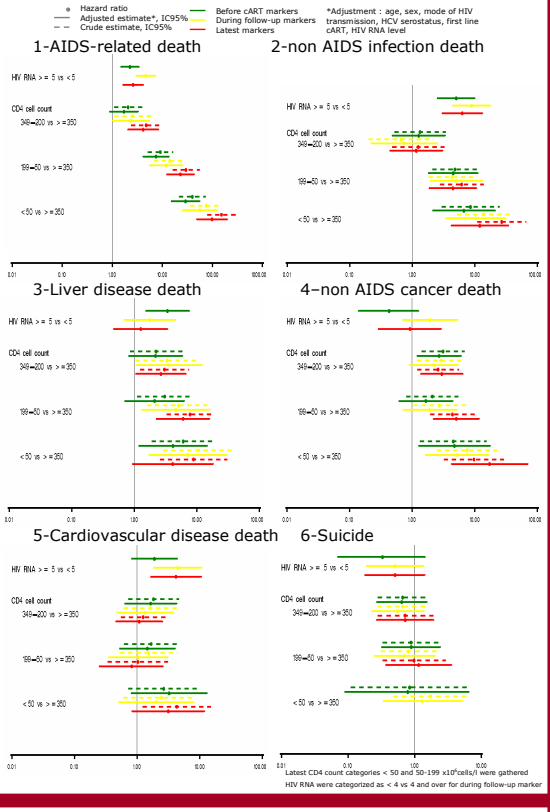
Table 2: Causes of deaths

Patients outcomes	Number	%
Censored patients	9261	-
Causes of death		
AIDS-related death	158	26.5
Non AIDS infection	50	8.4
Liver disease	46	7.7
Non AIDS cancer	46	7.7
Cardiovascular disease	36	6.0
Suicide	38	6.4
Substance abuse	34	5.7
Violent	20	3.3
Respiratory disease	20	3.3
Other causes	43	7.2
Unknown causes	106	17.8
Dead patients overall	597	100.0

More than half of the 597 deaths were non AIDS-related

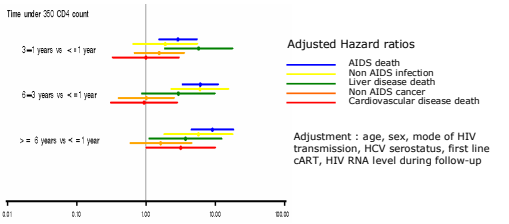
Results (2) latest and Nadir CD4 counts

Figure 1 : Cause specific Hazard Ratios for nadir CD4 and latest CD4 counts



Results (3) Time under 350 cellsx10^6/l

Figure 2 : Cause specific Hazard Ratios for time spent under 350 CD4 cell count



Comments - conclusion

- ➔ There is a **clear relationship of either latest or nadir CD4 count** with four specific causes of death : those which were AIDS-related, and among those which where not AIDS-related: severe infections, liver diseases, malignancies. A clear gradient effect is observed for these causes
- ➔ Deaths due to cardiovascular disease are not immunodeficiency-related nor suicide
- ➔ These results are consistent when we considered the **relationship with time spent under 350 cells** x10^6/l with a gradient effect
- ➔ **A higher HIV RNA** before cART was associated with AIDS deaths, non AIDS infections and liver diseases deaths
- ➔ These results plead for **earlier initiation of antiretrovirals** to reduce the impact of the most frequent specific causes of death
- ➔ **Morbidity related to non AIDS-conditions** should be **explored in observational studies** in order to better describe the current disease history under cART

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