Poster O-143

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Risk of Cause-specific Deaths over Calendar Time and according to Cumulative Exposure to Combination Antiretroviral Therapy (cART)

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BACKGROUND

Despite the pronounced benefit from use of cART adverse effects that could limit the overall long term treatment benefit remain possible.

It is recognised that HIV itself is associated with an increased risk of a range of conditions beyond AIDS itself.

Despite this complication, investigating changes in the rate of death from non-AIDS causes with increased cART exposure may provide further insight into whether there are cumulative toxicities of cART.

METHODS

- Patients were followed from enrolment into EuroSIDA until last follow-up visit or death.
- Non-AIDS related deaths were classified into: non-AIDS related infections (NARI), liver related (LRD) (hepatitis, non-hepatitis liver failure and liver cancer), non-AIDS defining malignancies (NADM), cardiovascular disease (CVD), violent (including an accident or violence, suicide, euthanasia, substance abuse or overdose), other (causes associated with < 20 deaths) or unknown (deaths with insufficient information to determine its cause)
- Incidence rates (IR) of death were calculated per 1000 person-years of follow-up (PYFU) in 3 calendar periods <1997, 1997-2001(reference), ≥2002 and by time of exposure to cART: <2, 2-4 (reference), 4-6, >6 years. The effect of date of starting cART on the association between exposure to cART (grouped as <2, 2-4 and >4) and risk of death was also investigated
- Any time when the patient was off cART was not counted as exposure time. cART was defined as receiving ≥3 antiretrovirals after 1/1/1996
- Poisson regression models were fitted for each cause of death separately, adjusting for factors significant (p<0.01) in univariate analysis. Variables investigated were age*, gender, ethnic origin, HIV transmission group, region of Europe, smoking status*, diabetes*, hypertension*, hepatitis B and C status*, CD4 count*, viral load*, any previous AIDS defining illnesses (*time updated). Year of follow-up was not included in the multivariate model as it was highly correlated with time on cART

RESULTS

BASELINE CHARACTERISTICS

- The baseline characteristics of the 15444 patients included in the analysis are shown in **table 1**
- During 87972 PYFU, 2744 patients died. Of the deaths, 1426 (52%) were non-AIDS related with the distribution: NARI 18%, LRD 18%, NADM 10%, CVD 11%, violent 11%, other 11% and unknown 22%

Table 1

Baseline characteristics

All patients (N, %)		15444	100%
Gender (N,%)	Male	11512	74.5%
Ethnic origin (N, %)	White	13559	89.2%
HIV exposure group (N, %)	Homosexual	6071	39.3%
	IDU	3834	24.8%
	Heterosexual	4393	28.4%
Prior AIDS diagnosis (N,%)		4365	28.3%
Started cART (N,%)		10519	68.1%
Enrolled into EuroSIDA (N,%)	<1997	4188	27.1%
	1997-2002	4939	32.0%
	≥2002	6317	40.9%
Age (median, IQR)		36	31-44
CD4 count (media, IQR)		307	160-462
Viral load (median, IQR)		2.70	1.70-4.23

Baseline was defined as date of enrolment into EuroSIDA; 349 patients had a missing CD4 count at enrolment and 5459 patients had a missing viral load

Figure 1

The adjusted incidence rate ratios for specific causes of death by calendar time

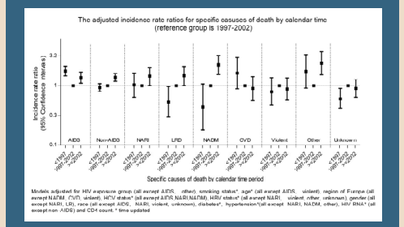
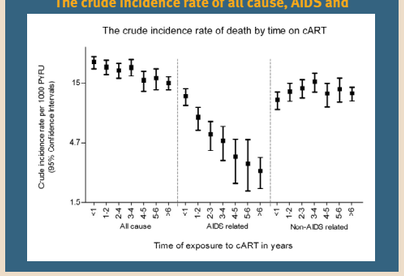


Figure 2

The crude incidence rate of all cause, AIDS and



RESULTS

Trends in cause-specific mortality during follow-up time:

- The crude IR declined from <1997 to ≥2002 for all cause (from 170.6 to 15.8 per 1000 PYFU, p<.0001), AIDS (118.3 to 4.4 per 1000 PYFU) and non-AIDS related deaths (52.2 to 11.4 per 1000 PYFU)
- The crude IR showed a decline over calendar time, but after adjustment (including adjusting for time updated CD4 count and HIV RNA viral load) figure 1 shows that there is a trend towards an increased rate over the three calendar periods, for some specific causes of non-AIDS related death (**Figure 1**)

Cause-specific mortality in patients exposed to cART:

- Among 11982 patients on cART, 1283 died within 68990 PYFU. During this time 407 AIDS-related deaths and 876 non-AIDS related deaths were observed.
- The crude IR for both all-cause and AIDS related mortality decreased with time of exposure to cART, but this was not seen for non-AIDS related deaths (**Figure 2**)
- The risk of non-AIDS related death was lower in the first two years from starting cART as compared with 2-4 years on cART (adjusted incidence rate ratio (IRR) = 0.64 [0.52-0.80]). This trend with respect to specific causes of death remained significant for LRD (0.45 [0.30-0.67]), CVD (0.55 [0.33-0.93]), other (0.57 [0.33-0.99]) and unknown (0.65 [0.43-0.98]), but not for NARI, NADM or violent death
- There was no significant change in the risk of cause-specific death between 2-4 years of exposure and any longer exposure time for any of the specific causes of death (**Figure 3**)

Starting cART in different time periods:

- For patients initiating cART prior to 1997, and to a lesser extent between 1997-2002, the risk of non-AIDS related death was significantly lower in the first two years after cART initiation compared to 2-4 years on cART (**Figure 4**)
- This relationship was not seen in patients starting ART in more recent years (**Figure 4**)

CONCLUSIONS

- In cART-experienced patients who started treatment after 2002, there was no change in risk of non-AIDS related death with increasing cART exposure after accounting for the latest CD4 count, viral load and other factors. In those starting cART earlier than 2002, there was a lower risk of non-AIDS related death in the first two years after starting cART, but there was again no change in risk thereafter

Figure 3

The adjusted incidence rate ratios for specific cause of death by cumulative exposure to cART

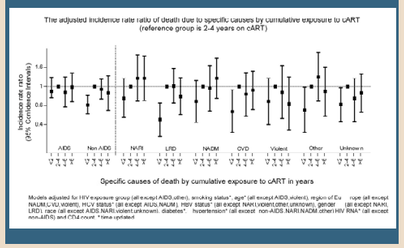
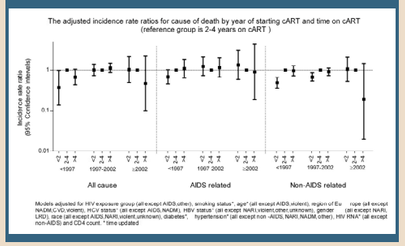


Figure 4

The adjusted incidence rate ratios of death stratified by year of starting cART and time on cART



EuroSIDA study group

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