

Serious non-AIDS events are increasingly more common than AIDS events in the HIV-1 cART treated population

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Background

HIV-1 suppressing combination antiretroviral therapy (cART) increases the life expectancy of infected patients significantly, although still not to that of the age and gender matched general population. As a result patients increasingly experience serious non-AIDS diseases traditionally associated with older age in the uninfected population.

Objective

To study changes in AIDS and serious non-AIDS events over time since cART introduction in the registered HIV-1 infected population in the Netherlands.

Methods

Patients

HIV-1 infected patients aged 16 years or more who started cART between 1 July 1996 and 31 December 2008 were selected.

Outcome

- Time to death (causes of death classified according the CoDe scheme).
- Incidence of fatal and non-fatal AIDS and serious non-AIDS events: liver events (liver fibrosis, cirrhosis or hepatocellular carcinoma), renal insufficiency (chronic or acute), diabetes mellitus, myocardial infarction, cerebrovascular accident, osteoporosis and non-AIDS malignancies (excluding basal and squamous cell carcinoma).

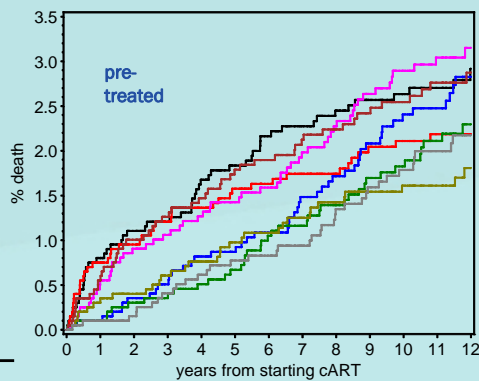
Statistical analyses

The incidence from serious non-AIDS events was calculated from the start of routine data collection of the event under question. Reported 95% confidence intervals (CI) are based on the Poisson distribution.

Results

- During 69738 person-years of follow-up after initiation of cART
 - 1103 of 11,724 patients died (15.8 deaths per 1000 py of follow-up, 95% CI 14.9-16.8). The most frequently recorded cause of death was AIDS (371 deaths), non-AIDS defining malignancy was the most frequent death due to non-AIDS causes (152 deaths).
 - 1637 patients were diagnosed with AIDS (26.1/1000 py, 95% CI 24.8-27.4)
 - 1042 patients had a serious non-AIDS defining event (23.4/1000 py, 95% CI 24.8-27.4) (from 2002 onwards).
- The cumulative incidence of AIDS-defining infections and cancers in pre-treated patients continued to rise with increasing time after first starting cART, whereas in naive patients the cumulative incidence of these causes of death levelled off after the first 3 years after starting cART, Figures 1.
- The incidence of both AIDS and non-AIDS events was highest in the first year following the start of cART and was 79.6/1000 PY (95% CI 74.4-85.1) and 32.3 (27.7-37.3), respectively ($p < 0.0001$). From 3 years after cART initiation onwards, non-AIDS events were more common than AIDS events, see Figure 2.

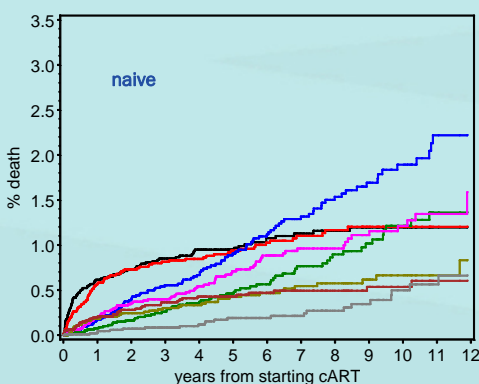
Figure 1. Cumulative incidence curves of death after starting combination antiretroviral therapy (cART) in 1975 pre-treated (top) and 8159 ART-naïve patients (bottom).



Legend:

Death due to:

- AIDS-defining infections —
- AIDS-defining cancers —
- non-AIDS-defining cancers —
- non-AIDS-defining infections —
- cardiovascular complications —
- suicide, euthanasia or violence —
- death due to AIDS (unspecified) —
- liver failure in combination with HCV or HBV co-infection —



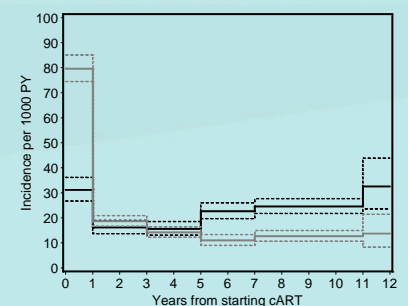
Incidence per 1000 person-years of follow-up

	Total diagnoses	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008								
Any AIDS event	1637	155.8	67.5	41.2	35.4	28.2	26.2	25.2	24.8	22.6	25.3	20.4	17.8	17.1								
AIDS dementia complex / HIV encephalopathy	99	0.0	2.5	1.4	3.0	1.4	1.6	0.4	1.8	1.2	1.8	1.1	1.2	1.5								
Cryptococcosis	45	0.0	0.5	0.7	1.1	0.9	0.8	1.4	0.5	0.9	0.4	0.3	0.7	0.3								
Herpes simplex virus	102	11.1	3.0	2.7	2.2	1.2	1.2	0.7	1.4	1.3	1.5	2.0	1.3	0.4								
Kaposi sarcoma	217	6.6	12.3	4.1	3.9	2.6	3.1	2.9	2.9	1.8	2.9	4.4	2.1	2.1								
Disseminated mycobacterium disease	94	15.5	5.4	3.1	2.2	1.7	1.4	0.7	0.6	0.9	1.1	1.1	1.2	0.3								
Other mycobacterium	57	6.6	1.5	1.4	2.2	2.1	1.0	0.9	0.3	0.4	0.5	0.1	0.6	0.6								
Pneumocystis jiroveci (carinii) pneumonia	179	4.4	6.4	4.8	5.0	3.6	2.5	3.6	1.6	2.2	2.0	1.6	1.2	2.7								
Recurrent pneumonia	177	6.6	2.5	2.7	2.2	2.4	3.9	2.3	3.1	2.8	2.6	1.4	3.0	2.3								
Progressive multifocal leucoencephalopathy	49	4.4	1.5	0.3	0.8	1.7	0.8	0.9	0.3	0.4	0.4	0.8	0.8	0.4								
Cerebral toxoplasmosis	103	13.3	3.0	3.1	2.5	1.9	2.3	0.7	2.3	1.6	1.6	0.8	0.8	0.0								
HIV wasting syndrome	75	2.2	2.0	1.7	2.5	1.7	0.6	1.2	0.6	0.6	1.2	0.9	0.7	0.9								
Candidiasis	353	31.0	12.9	7.6	6.7	5.0	6.6	4.7	5.2	3.4	4.9	5.1	3.5	3.6								
Cytomegalovirus infection	170	46.6	8.9	2.4	3.1	3.3	2.3	2.0	2.3	2.7	1.6	1.8	1.3	1.0								
Non-Hodgkin lymphoma	172	15.5	6.9	5.8	1.9	1.9	1.2	2.1	2.9	1.9	3.7	2.0	1.5	1.7								
Tuberculosis	185	6.6	3.4	3.8	2.5	2.4	2.5	3.9	3.2	2.7	3.1	2.4	1.9	1.9								
Any other CDC-C events*	91	11.0	5.9	2.7	2.2	2.9	1.4	0.7	1.1	0.7	1.5	0.9	0.4	0.3								
Any serious non-AIDS event	997							22.0	22.9	20.8	23.7	24.5	26.7	22.4								
Renal insufficiency	244							9.3	8.1	6.2	4.1	4.0	5.9	3.7	7.2	3.9	3.5	4.0				
Liver event	262							4.8	4.2	3.4	3.1	4.9	3.4	4.0	5.3	4.1	3.7	3.5				
Diabetes mellitus	307							6.5	7.5	5.3	5.2	4.7	5.6	3.6	4.5	5.0	3.6	2.6				
Myocardial infarction	162									4.1	2.1	4.3	3.1	3.0	2.6	2.5	2.5	2.6				
Osteoporosis	82											1.0	1.8	1.5	1.5	1.8	1.9	1.9				
CVA	106											2.3	1.6	1.6	2.7	1.6	1.7	1.3				
Non-AIDS defining malignancy	322											3.2	3.0	1.9	1.4	5.7	3.9	5.6	5.3	6.4	6.4	5.9

Table 1. Incidence of specific AIDS and serious non-AIDS events per 1000 person years of follow-up per calendar year. CVA: cerebrovascular accident.

* Included are events with less than 20 diagnoses: cryptosporidiosis infection (19 diagnoses), histoplasmosis (19 diagnoses), invasive cervical carcinoma (11 diagnoses), microsporidiosis (10 diagnoses), isosporiasis (4 diagnoses), Leishmaniasis (4 diagnoses), salmonella septicaemia (2 diagnoses), extrapulmonary pneumocystis (1 diagnosis) and unspecified events (21 diagnoses).

Figure 2. Incidence per 1000 person years of follow-up (95% confidence interval) of first AIDS diagnosis (grey line) and first diagnosis of any serious non-AIDS event (black line) after starting cART.



- Table 1 shows that whereas the incidence of any AIDS event per calendar year showed a decreasing trend, the incidence of the serious non-AIDS events between 2002 and 2008 was more or less stable ($p = 0.62$, test for trend).
- The incidence of AIDS in 2008 was 17.1/1000 py (14.2-20.5) compared to 22.4/1000 py (19.0-26.1) for any of the serious non-AIDS events.
- Overall, the most commonly diagnosed AIDS event was candidiasis infection (353 diagnoses, of which 338 were esophageal candidiasis), followed by Kaposi sarcoma (217 diagnoses).
- Non-AIDS defining malignancies were the most common serious non-AIDS event and showed an increasing incidence over time ($p < 0.0001$, test for trend). Incidence in 2008 of 5.9/1000 py (4.3-7.9). In contrast, the incidence of diabetes mellitus showed a decreasing trend over time ($p = 0.0003$).

Conclusion

From 3 years after first starting cART onwards, the incidence of serious non-AIDS events was higher than AIDS. In 2008 serious non-AIDS events were more common than AIDS events in the cART treated HIV-1 population.