Initiation of combined antiretroviral therapy for HIV infection and the risk of non-AIDS diseases

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Background

An association between immunodeficiency, HIV RNA level, and the risk of non-AIDS diseases has been previously reported for patients treated with combination antiretroviral therapy (cART).

- But therapy could confound this association by increasing the risk via adverse effects and simultaneously reverse the harm by restoring immunity.
- In addition, the range of RNA level is limited in treated patients.

Objective: to investigate whether the association between CD4 counts, RNA level and non-AIDS diseases before start of cART remains the same with after cART.

Methods

Study population

- 9777 patients, diagnosed with HIV in or after 1998, were selected from the ATHENA national cohort. Patients should have at least one CD4 count and RNA before cART.
- Follow-up started at the first available CD4 count and censored at either the occurrence of the events interested, or end of the follow-up.

Outcome

- four newly diagnosed non-AIDS endpoints (fatal and non-fatal) were considered.
  - cardiovascular disease (CVD): myocardial infarction, stroke, invasive coronary procedures
  - renal disease (RRD): acute and chronic renal failure
  - liver disease (LRD): fibrosis, cirrhosis, hepatocellular carcinoma
  - overall (All): combination of non-AIDS events abovementioned

Statistical analyses

- Poisson regression models were used to compare the effect of CD4 and RNA on non-AIDS events before and after cART.
- CD4, RNA level and age were included as time-updated variables.
- Both univariate and multivariate analyses were conducted; the latter were adjusted for age, gender, diabetes, HBV/HCV co-infection, CDC stage, smoking, alcohol abuse and hypertension.

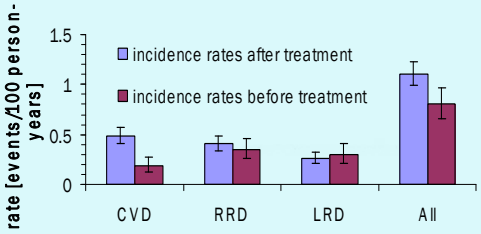
Results

Table 1. Characteristics of the study population

N=9777		N (%) / median (IQR)
Gender, male	7732	79.1
Region of origin		
Netherlands	5487	56.1
Sub-Saharan Africa	1805	18.5
Disease stage at baseline		
CDC-B	622	6.4
CDC-C	934	9.6
Hepatitis B co-infection	404	4.1
Hepatitis C co-infection	249	2.5
Diabetes mellitus	158	1.6
History of alcohol abuse	529	5.4
Smoking status		
never	3125	32.0
current or former	4271	43.7
unknown	2381	24.4
Patients no. never on cART	2299	23.5
	at entry of study	**at start of cART**
Age (years) at entry	37.1 (30.2-44.3)	38.6 (31.8-45.9)
CD4 counts (cells/mm^3)	350 (170-550)	215 (101-310)
Log_{10}RNA plasma level	4.8 (4.1-5.2)	5.0 (4.5-5.4)
Follow-up time (years)	0.4 (0.1-2.1)	3.5 (1.5-6.6)

Non-AIDS incidence rates

Figure 1. comparison of non-AIDS incidence rate before and after cART



No. of non-AIDS events				
before cART	25	48	41	110
after cART	151	126	81	335

Figure 1. showed the incidence before start of cART was lower than after start for overall (0.81 per 100 person-years vs. 1.10, p=0.005) and for CVD (0.18 vs. 0.49, p<0.001)

Non-AIDS events with latest CD4 counts

Figure 2. effect comparison of CD4 on non-AIDS events before and after cART

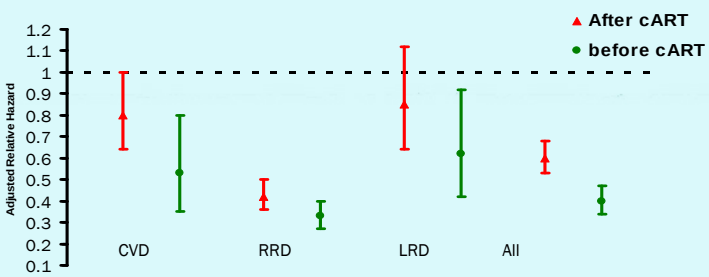


Figure 2. showed a higher log-transformed CD4 count was associated with lower risk of non-AIDS events. But only CD4 before cART, not after cART, was in association with LRD (RR 0.62, 0.42-0.92). The effect of CD4 before cART on renal disease (RR 0.33, 0.27-0.40) was significantly stronger than that after cART (RR 0.42, 0.36-0.50), the same with combined endpoint.

Non-AIDS events with latest RNA levels

Table1. Comparison of the effect of HIV RNA on non-AIDS events.

		Adjusted Relative Risk (95% Confidence Interval)			
		cardiovascular disease	renal disease	liver disease	combined endpoint
latest RNA (copies/ml)	≤10^3	7.02 (1.46-33.7)	0.80 (0.37-1.74)	0.83 (0.31-2.25)	1.47 (0.85-2.52)
	10^3-10^5 after	7.29 (1.34-39.7)	1.15 (0.45-2.93)	1.48 (0.46-4.78)	2.21 (1.17-4.19)
	10^3-10^5 before	3.81 (0.87-16.6)	0.65 (0.34-1.24)	0.85 (0.37-1.96)	1.03 (0.64-1.65)
	>10^5 after	16.9 (2.93-97.5)	1.47 (0.52-4.14)	2.62 (0.67-10.2)	3.20 (1.56-6.58)
	>10^5 before	1	1	1	1

In adjusted models, compared to RNA > 10^5 copies/ml before cART, RNA after cART was associated with higher risk of CVD (RR 7.29, 95%CI 1.34-39.7 if RNA ≤ 10^3; RR 6.89, 1.27-37.5 if 10^3 <RNA ≤ 10^5; RR 16.0, 2.78-92.3 if RNA > 10^5;), Similar trend was observed with the combined endpoint. No association was found among RNA, renal disease and LRD.

Conclusions & discussion

- Higher CD4 counts are more strongly related with non-AIDS diseases before start of cART than thereafter.
- However, despite more variation in HIV RNA before cART, there was no significant association with incidence of non-AIDS events, presumably because of the paucity of events before cART.