

Incomplete immune recovery on HAART is associated with significant more cardiovascular events and a trend for more non-AIDS related malignancies in Dutch ATHENA cohort



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Background

- Despite adequate suppression of plasma HIV RNA, incomplete immune recovery occurs in 5-15% of patients starting HAART.
- Cardiovascular events (CVE) and non-AIDS related malignancies (NAM) may be related to immunodeficiency.
- We studied the relation between incomplete immune recovery after two years of virological successful HAART and clinical outcome, the occurrence of CVE and NAM.

Methods

Inclusion criteria

- Antiretroviral therapy naive patients (≥ 16 years) starting HAART from 1998 onwards, Initial suppression to <500 copies/ml within 9 months after first starting HAART and no therapy interruptions longer than 2 weeks.

Exclusion criteria

- RNA >500 copies/ml between 18-24 months after start HAART, pregnancy, combination tenofovir with didanosine and use of immunosuppressive medication

Baseline: grouping according to CD4 cell count after 2 years

- Baseline was defined as the timepoint 24 months after starting HAART
- At baseline, patients were grouped based on immune recovery during HAART
- The last two CD4 cell counts before baseline were used for this purpose, resulting in the groups:
 - CD4 cell count < 200 cells/μl
 - CD4 cell count 200-350 cells/μl
 - CD4 cell count 350-500 cells/μl
 - CD4 cell count > 500 CD4 cells/μl

Outcome measures (1)

- Assessment of general clinical outcome: time from baseline to occurrence of a combined endpoint (first of any of CVE, NAM and AIDS-related malignancy, AIDS or death).

Variable	CD4 <200	CD4 200-350	CD4 350-500	CD4 > 500	Total
Number [n (%)]	200 (6.5)	646 (21.0)	1414 (46.0)	811 (26.4)	3071 (100.0)
Male gender [n (%)]	177 (88.5)	545 (84.3)	1163 (82.3)	677 (83.5)	2562 (83.4)
Age (years) #	45 (38-54)	42 (36-49)	40 (35-47)	39 (34-46)	41 (35-48)
Baseline CD4 (cells/μL) #	145 (123-165)	255 (220-289)	425 (370-485)	677 (605-797)	425 (300-570)
CD4 nadir (cells/μL) #	30 (10-70)	76 (20-130)	170 (90-228)	260 (190-341)	160 (70-240)
HIV-RNA at start HAART (log copies/ml) #	5.1 (4.8-5.6)	5.0 (4.7-5.4)	5.0 (4.6-5.4)	5.0 (4.6-5.5)	5.0 (4.6-5.4)
Regimen containing PI [n (%)]	62 (31.3)	219 (34.4)	402 (28.8)	271 (33.8)	954 (31.5)
Regimen containing NNRTI [n (%)]	113 (57.1)	354 (55.7)	857 (61.4)	427 (53.2)	1751 (57.7)
Transmission risk group [n (%)]:					
MSM	102 (51.0)	317 (49.1)	821 (58.1)	525 (64.7)	1765 (57.5)
Heterosexual	7 (3.5)	17 (2.6)	31 (2.2)	10 (1.2)	65 (2.1)
IDU	66 (33.0)	248 (38.4)	462 (32.7)	238 (29.4)	1014 (33.0)
Region of origin [n (%)]:					
Western Europe/North America	139 (69.5)	380 (58.9)	902 (63.8)	574 (70.8)	1995 (64.9)
Subsaharan Africa	30 (15.0)	129 (20.0)	235 (16.6)	101 (12.5)	495 (16.1)
Caribbean/Latin America	20 (10.0)	73 (11.3)	166 (11.7)	83 (10.2)	342 (11.1)
Risk factors [n (%)]:					
Smoking*	84 (59.15)	256 (58.5)	522 (55.6)	381 (65.5)	1243 (59.2)
CVE in family*	14 (12.4)	30 (9.5)	46 (6.7)	37 (8.6)	127 (8.2)
Alcohol abuse	17 (8.5)	44 (6.8)	97 (6.9)	60 (7.4)	218 (7.1)
CVE before baseline	2 (1.0)	13 (2.0)	21 (1.5)	7 (0.9)	43 (1.4)

Table 1. Baseline characteristics according to CD4 strata. #median (IQR), *percentage of known records

Outcome measures (2)

- Time from baseline to occurrence of first CVE (coronary bypass, coronary stenting or angioplastic, fatal and non-fatal myocardial infarction and cerebrovascular attack (CVA).
- Time from baseline to occurrence of first NAM (all malignancies except Kaposi sarcoma, cervix carcinoma, non-Hodgkin lymphoma).
- In order to assess further immune recovery during follow up, time from baseline to achieving a CD4 cell count increase of 100 cells/μl from baseline was analyzed.
- Survival analysis: Kaplan Meier (KM) estimates and unadjusted and adjusted Cox proportional hazard models.
- For assessment of predictors of incomplete immune recovery logistic regression models were used.

Results

Baseline characteristics (table 1)

- In total 3071 patients were included, duration of total follow up was 10,956 patient years.
- Poor immune recovery (< 200 CD4 cells/μl after two years of fully suppressive HAART) was associated with older age (p<0.0001), lower CD4 nadir (p<0.0001), male gender (p=0.046), lower plasma HIV-RNA at start HAART (p=0.009) and antiretroviral regimen at baseline containing NNRTI (compared with PI; p=0.0002).
- Odds ratios (OR): older age 1.04 (95% CI 1.02-1.06), higher CD4 nadir 0.98 (0.97-0.98), female gender 0.55 (0.31-0.99), higher plasma HIV-RNA 0.74 (0.59-0.93) and use of PI 0.48 (0.32-0.70). Estimated OR 0.09 per 100 nadir CD4 cell increase, 1.21 per 5 years increase in age and 0.74 per 1 log increase in plasma HIV-RNA.

Assessment of clinical outcome: combined endpoint (Figure 1A and table 2)

- During follow-up in total 198 'combined' events occurred.
- In the group with CD4 <200 significantly more events occurred (overall log rank, p<0.0001).
- Hazard ratios (HR) were adjusted for age, gender, smoking, antiretroviral regimen (PI versus NNRTI), family history for cardiovascular diseases, alcohol abuses, plasma HIV-RNA at start HAART, transmission category, CVE before baseline and region of origin.

Cardiovascular events (figure 1B and table 2)

- During follow-up in total 58 cardiovascular events occurred.
- Significantly more cardiovascular events occurred in the group with <200 CD4 cells/μl (overall log rank, p=0.02).
- Hazard ratios were adjusted for age, gender, smoking, antiretroviral regimen (PI versus NNRTI) and positive family history of cardiovascular diseases.

Non-AIDS related malignancies (figure 1C and table 2)

- During follow-up in total 36 non-AIDS related malignancies developed.
- There was a non-significant trend for shorter time to NAM in the group with CD4 <200, compared with CD4 350-500 (p=0.07) and CD4 >500 (p=0.11) (overall log rank, p=0.25).
- Hazard ratios were adjusted for age, smoking and alcohol abuse.

Persistent poor immune recovery during follow-up (figure 1D and table 2)

- During follow up, 2048 patients achieved an increase of 100 CD4 cells.
- A significantly longer time to achieve a CD4 cell count increase was observed in the group with CD4 <200 (overall log rank, p<0.0001).
- Hazard ratios were adjusted for age, gender, antiretroviral regimen (PI versus NNRTI), plasma HIV-RNA at start HAART, region of origin and alcohol abuse.

Endpoint [HR (95% CI)]	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
Combined	1.00	0.67 (0.40-1.10)	0.57 (0.36-0.92)	0.46 (0.27-0.77)
CVE	1.00	0.45 (0.18-1.08)	0.70 (0.33-1.47)	0.54 (0.23-1.25)
NAM	1.00	0.84 (0.29-2.47)	0.57 (0.20-1.63)	0.63 (0.21-1.91)
Increase of 100 CD4 cells	1.00	1.55 (1.25-1.93)	1.55 (1.26-1.90)	1.74 (1.40-2.14)

Table 2. Adjusted hazard ratios for the various endpoints, compared with patients with < 200 CD4 cells/mm3 after 2 years virological successful HAART.

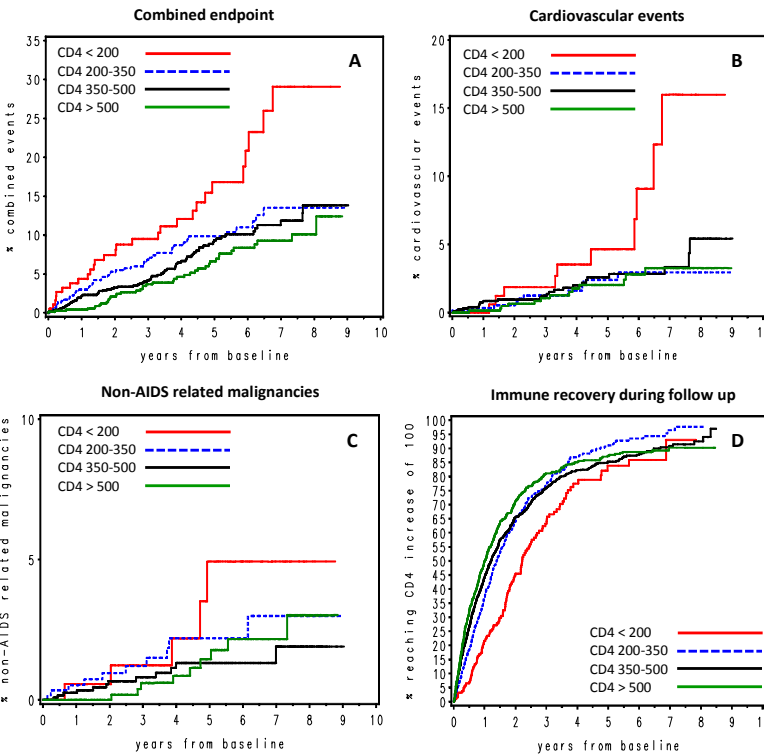


Figure 1A-D: Kaplan-Meier curves according to CD4 recovery of time to 'combined' events, cardiovascular events, non-AIDS related malignancies and to achieve a CD4 cell count increase of 100.

Conclusions

- In this cohort older age, lower CD4 nadir and use of NNRTI-based regimen were predictors for an incomplete immune recovery of <200 CD4 cells/μl after 2 years of fully suppressive HAART.
- Incomplete immune recovery was associated with poorer immune recovery and poorer clinical outcome during further follow up.
- In the group with <200 CD4 cells/μl at baseline more cardiovascular events and a trend for more non-AIDS related malignancies was observed.
- Because of the small number of cardiovascular events and non-AIDS related malignancies, analysis of larger, combined cohorts is needed to support this data.