

Risk of progression to AIDS or death in relation to CD4 cell levels in HIV- infected patients with sustained viral response to cART

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Background

- More than 90% of patients can achieve full suppression within a year of starting modern cART
- Information on prognosis in these patients in relation to CD4 cell recovery is therefore important
- We assessed the risk of new AIDS events or death in successfully treated patients from the COHERE 2010 database merger

Method - suppression episodes

- Accumulate episodes of viral suppression while on cART
- Definition of viral suppression episode
 - Start
 - second of 2 consecutive viral loads <50 copies/ml
 - End
 - viral load >500 copies/ml
 - first of two consecutive measurements between 50-500 copies/ml
 - cART interruption
 - administrative censoring

Method - patients inclusion

- At least one suppression episode
- Pre-specified covariates:
 - CD4 cell count within 6 months prior to the start of an episode or within an episode
 - age, gender, iv drug use, viral load, co-infection HBV & HCV, cART, and number of prior cART regimens
- Patients could contribute more than one episode, but were not at risk between episodes

Method - outcomes and model

- Outcomes
 - Primary: time to first new AIDS event or death
 - Secondary: time to death
- Cox proportional hazards models to estimate the hazards of progression to AIDS or death per 100 cells/ μ L increase in CD4 cell count
- CD4 cell counts were updated over time
- CD4 cell count is represented by a linear spline with three knots at 200, 350 and 500 cells/ μ L

Results - baseline characteristics

Patient characteristic	Included (n=66,147)	Excluded (n=110,438)
Age, years - median [IQR]	37 [32, 44]	35 [28, 41]
Female - %	27	29
Ever diagnosed with AIDS - %	26	25
Transmission by drug use - %	14	17
CD4 cell count, cells/ μ L - median [IQR]	396 [256, 565]	
Viral load \log_{10} copies/ml - median [IQR]	4.6 [3.5, 5.2]	
cART category - %		
- NNRTI	34	
- Boosted PI	30	
- Single PI	25	
- Other	11	

Results - suppression episodes and CD4 cells

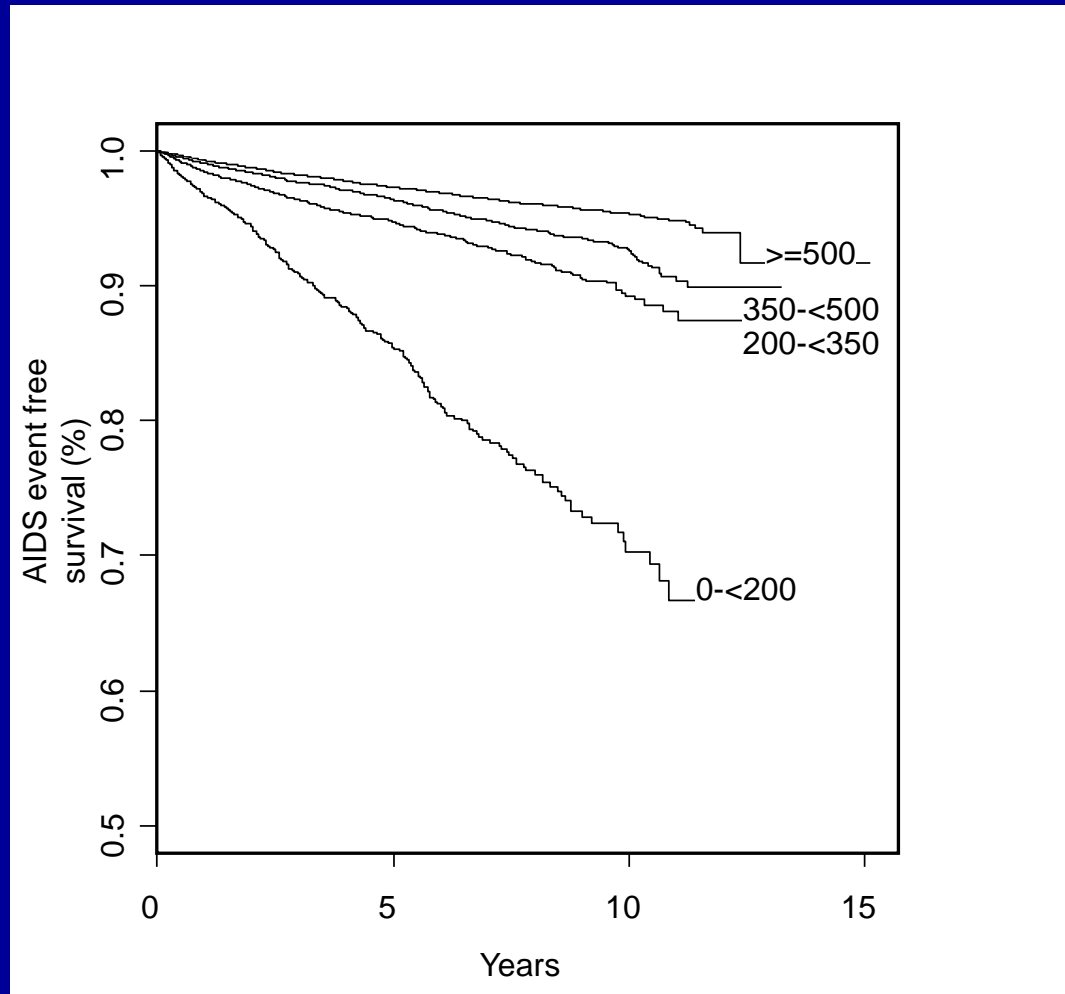
Single suppression episode	74% of patients
Median length of episodes (years)	1.7 (IQR 0.7, 3.5)
Median length suppressed while on cART per patient	2.7 years (IQR 1.2, 5.1)
CD4 cell category, cells/ μ L, at first suppression period	
<50	1 %
50 - <200	15 %
200 - <350	26 %
350 - <500	25 %
\geq 500	34 %

Results - event rates per 1000 years suppressed

Most recent CD4 cell count (cells/ μ L)	First new AIDS event or death from any cause (no. of events)	Death from any cause (no. of events)
<50	94.9 (54)	64.8 (38)
50-<200	30.5 (489)	20.0 (325)
200-<350	12.0 (548)	6.9 (318)
350-<500	7.9 (487)	3.8 (240)
\geq 500	5.2 (679)	2.4 (315)

Results - probability of event free survival over time

For hypothetical patients whose CD4 cell count is constant while on cART with a suppressed viral load



Results - Cox model hazard ratios (95 % CI) per 100 cells/ μ L increase

For primary and secondary outcomes adjusted for covariates

CD4 cells/ μ L as a linear spline	Time to first new AIDS event or death (1838 events)	Time to death from any cause (1000 events)
0 - <200	0.35 (0.30-0.40)	0.32 (0.27-0.39)
200 - <350	0.81 (0.71-0.92)	0.75 (0.63-0.89)
350 - <500	0.74 (0.66-0.83)	0.68 (0.58-0.80)
≥ 500	0.96 (0.92-0.99)	0.98 (0.93-1.03)

Results - Cox model hazard ratios (95 % CI)

For primary and secondary outcomes adjusted for covariates

Reduced model CD4 cells/ μ L as a linear spline	Time to first new AIDS event or death (1838 events)	Interaction term for constant effect over time
0 - <200	0.21(0.19-0.24)	0.51 (0.48-0.54)
\geq 200	0.92 (0.90-0.94)	1.02 (1.00-1.05)

Discussion I

- In virologically suppressed patients increase in CD4 cells reduces the risk of AIDS or death
 - Largest benefit in patients with CD4 cells <200 cells/ μL
 - Similar benefit in patients with CD4 cells 200 - 350 cells/ μL or 350 - 500 cells/ μL
- These effects are robust
 - narrow CIs
 - stable in sensitivity analysis
 - no apparent difference between continuous or episodic viral suppression

Conclusions

- In virologically suppressed patients
 - Lack of increase in CD4 cell is relevant for prognosis and poorer outcome
 - <200 cells/ μL and no CD4 cell recovery risk of disease progression increases over time and therefore continued medical attention is needed
- Indirect evidence from this data for early initiation of cART

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