Immunological, virological and clinical changes during periods of transient viremia

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Background

In many patients on highly active antiretroviral therapy (HAART) who achieve sustained suppression of HIV-1 viral load to levels <50 copies/ml, transient episodes of low-level viremia ("blips") are observed. Our study aimed to investigate a possible relationship between viremia and immunological, virological and clinical changes during continuous treatment with HAART.

Methods

- 4447 adult patients were selected from the ATHENA national observational HIV cohort in the Netherlands who
  - initiated HAART whilst being therapy naïve.
  - had continuous treatment after starting HAART.
  - achieved initial success, defined as two consecutive HIV-RNA levels <50 copies/ml at least 2 weeks and at most 24 weeks apart.
- episodes of viremia started when HIV-RNA plasma levels rose >50 copies/ml and ended when they returned <50 copies/ml, which marked the start of another period of success. Periods of viremia were subdivided into low-level (50-1000 copies/ml) and high-level (>1000 copies/ml).
- during each period, changes in therapy, drug resistance in RT and protease, CDC-events and (therapy-related) adverse events were assessed.
- changes in $CD4^+$ and $CD8^+$ T cell counts were studied using mixed effects models.

Study population

N=4447	N	%
gender, male	3432	77.2
transmission risk group		
homosexual contact	2338	55.6
heterosexual contact	1623	36.5
injection drug use	124	2.8
region of origin		
the Netherlands (NL)	2522	56.7
sub-Saharan Africa (SSA)	868	19.5
at least one RNA >50 copies/ml	1283	28.9
at least one RNA >1000 copies/ml	301	6.8
	median	IQR
time T_0 to success (years)	0.8	0.5-2.0
age at T_0 (years)	39.3	33.4-46.1
RNA at T_0 (log_{10} copies/ml)	5.0	4.5-5.4
CD4 at T_0 (10^6 cells/l)	190	80-310
CD8 at T_0 (10^6 cells/l)	850	550-1240
CD4 at success (10^6 cells/l)	390	250-570
CD8 at success (10^6 cells/l)	921	646-1270
follow-up since success (person-years, py)	11,186	

IQR: inter-quartile range; T_0: start of HAART

RNA measurements after initial success

RNA category	<50	50-1000	>1000	total
# meas.	33981	2245	783	36552
	92.1%	6.0%	1.9%	100%
median # meas. per py (IQR)	3.04 (3.01-3.07)	0.199 (0.190-0.207)	0.064 (0.059-0.069)	3.30 (3.27-3.33)
median days to next RNA (IQR)	105 (86-133)	76 (35-105)	69 (40-101)	103 (84-131)
# periods	5993	1716	371	8080
	74.2%	21.4%	4.6%	100%

Characteristics of periods of success and viremia

	success N=5993		low-level viremia, N=1716		high-level viremia, N=371	
	N	%	N	%	N	%
origin						
NL	3464	57.8	1025	59.7	170	45.8
SSA	1097	18.3	278	16.2	117	31.5
RNA meas.						
1	973	16.2	1405	81.9	218	58.8
2	753	12.6	203	11.8	82	22.1
≥ 3	4267	71.2	108	6.3	71	19.1
no event	2679	44.7	1342	78.2	151	40.7
therapy change	2567	42.8	237	13.8	194	52.3
drug resistance	0	0	22	1.3	86	23.2
CDC-B event	125	2.1	13	0.8	4	1.1
CDC-C event	87	1.5	5	0.3	5	1.3
adverse event	2314	35.6	180	10.5	52	14.0
	median	IQR	median	IQR	median	IQR
duration (years)	1.3	0.5-2.8	0.2	0.1-0.3	0.2	0.1-0.4
CD4	460	318-640	480	320-680	360	250-528
CD8	925	680-1235	1012	750-1352	1042	818-1400
CD4 %	33.3	24.4-42.8	32.2	23.3-41.5	24.6	18.6-33.5
change per year	mean	95% CI	mean	95% CI	mean	95% CI
CD4	32	(30,34)	-4	(-34,27)	-80	(-107,-54)
CD8	-20	(-23,-0.02)	54	(-13,120)	57	(1,113)
CD4 %	1.76	(1.67,1.85)	-1.0	(-2.2,0.2)	-3.3	(-4.4,-2.2)

CI: confidence interval

- CD4 cell counts were similar during periods of success and low-level viremia (p=0.01), but were lower during high-level viremia (p<0.001); CD8 cell counts were similar between periods of low-level and high-level viremia (p=0.06), but lower during success (p<0.001).
- CD4 counts increased whilst CD8 counts decreased over time during success (p<0.001); CD4 counts decreased during periods of high-level viremia.
- low-level viremia: majority of periods short-lasting (93.7% ≤2 RNA measurements), without event and almost no resistance.
- high-level viremia: therapy changes and resistance were frequently observed; more frequent in sub-Saharan Africans.

Conclusions & discussion

- Short-lasting periods of low-level viremia are frequent but not clearly associated with selection of resistance and therapy mostly remains unchanged.
- In contrast, high-level viremia is frequently associated with resistance and often leads to therapy changes.
- The low incidence of resistance during low-level viremia suggests that leaving therapy unchanged during such periods is an acceptable strategy.
- The higher proportion of sub-Saharan Africans with high-level viremia might indicate that some of those periods are due to lack of adherence as sub-Saharan Africans are known to be less adherent and have less favourable virologic response.
- Low-level viremia cannot be explained by random viral load assay variations alone as CD8 cell counts are different from those during periods of success.

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