Persistent immune activation despite suppressive HAART is associated with higher risk for viral blips in HIV-1 infected individuals

Alexander Zoufaly[1]*, Jan G Kiepe[1]*, Sandra Hertling[1], Anja Hüfner[1], Olaf Degen[1], Torsten Feldt[2]
Stefan Schmiedel[1], Michael Kurowski[3], Jan van Lunzen[1]

1) Department of Medicine 1/Infectious Diseases Unit, University Medical Center Hamburg-Eppendorf, Germany
2) Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
3) HIV Laboratory Therapia, Auguste-Viktoria Clinic, Berlin, Germany

Introduction

Viral blips are thought to represent random biological variations around a steady state of residual HIV viremia and to lack clinical significance.

However, blips may be the consequence of shedding from activated immune cells and persistent immune activation has recently been linked with increased morbidity and mortality.

In this study we aimed to analyze the association between viral blips and systemic immune activation.

Methods

Patients from our HIV outpatient cohort were included in this nested case-control study if they developed a blip after having been on fully suppressive HAART for at least 180 days.

Cases were matched with controls without blips according to duration of time of complete viral suppression (CVS), age, sex, and CDC stage.

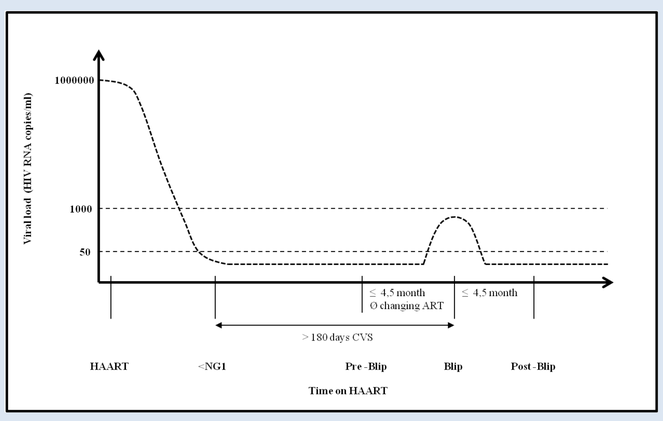

Figure 1: Blips were defined as intermittent episodes of detectable low-level HIV-1 viraemia >50 and <1000 copies/mL which are proceeded and followed by viraemia in the undetectable range. CVS: Complete viral suppression, HAART: Initiation of HAART, <NG1: First viral suppression, Pre-Blip: 3 month before index date, Post-Blip: 3 month after index date.

All used viral load assays (Amplicor and Taqman HIV-1 PCR) had, at least, a lower limit of detection of ≤50 HIV RNA cop/ml.

Flow cytometry was used to measure CD3, CD4, CD8, HLA-DR+, CD45RA+, CD16+, CD56, and CD19+ on longituninal blood samples from cases and controls.

Domain averaged areas under the curve were calculated for these cellular markers as well as C-reactive protein levels from first date of CVS until index date (date of viral blip or corresponding date in blip-free controls). A univariate and multivariable conditional logistic regression model was used to assess risk factors for viral blips.

Adherence to HAART was assessed by measuring prescribed NNRTI or PI plasma levels at index date in a subset of 57 patients who had available serum samples.

Results

Characteristics	Controls without blips (n = 82)	Cases with blips (n = 82)	p
Male sex*	66 (80.5)	66 (80.5)	1
Age in years, mean (SD) *	47.8 (12.4)	46.1 (11.9)	0.36
CD4 count at HAART initiation, median (IQR)	(n=77) 148 (44-249)	(n=75) 170 (43-310)	0.02
Viral load at HAART initiation, median log10 (IQR)	(n=77) 4.89 (4.29-5.48)	(n=63) 5.08 (4.40-5.64)	0.43
Duration of complete viral suppression (baseline to index date), median, IQR*	433 (243-952)	427 (252-1038)	0.28
Number of Regimen switches (baseline to index date)	1 (0-1)	0 (0-2)	0.83
CDC C Stage at index date*	35 (42.7)	35 (42.7)	1
Viral load at index date, median cop/ml (IQR)	<50	94 (70 - 150)	
Regimen at index date			0.05
NNRTI containing	49 (60.0)	33 (40.2)	
PI containing	22 (26.8)	32 (39.0)	
NNRTI+PI containing	6 (7.3)	13 (15.9)	
Other	5 (6.1)	4 (4.9)	

Table 1: Characteristics of patients with blip (cases) and without blip (controls). *matched variables

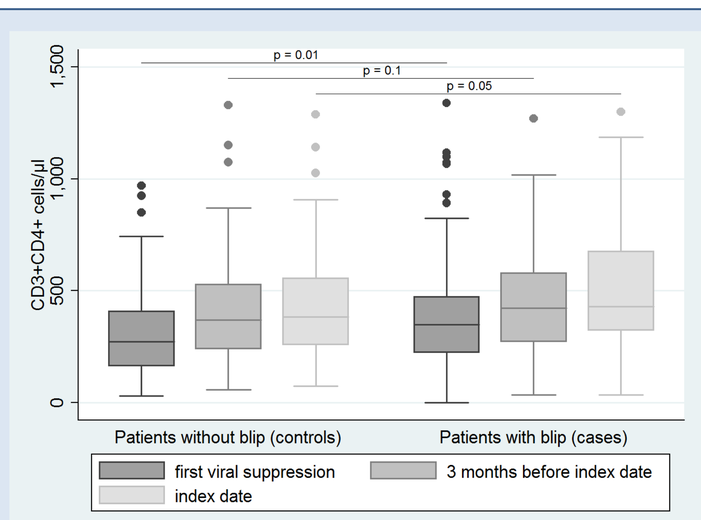

Figure 2: Frequencies of CD3+CD4+ T-helper cells at first viral load <50 cop/ml, 3month prior to index date, and index date in patients with blip and without blip

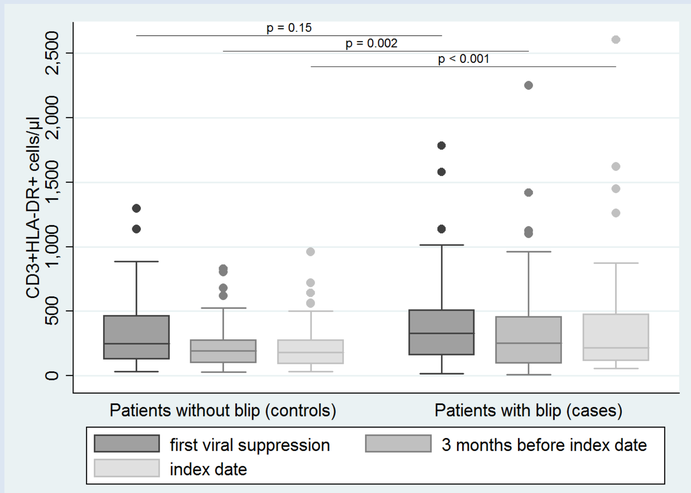

Figure 3: Frequencies of activated (HLA-DR+CD3+) lymphocytes at first viral load <50 cop/ml, 3month prior to index date, and index date in patients with and without blip

	univariate				multivariable			
	OR	95%CI		p	OR	95%CI		p
Total lymphocytes*	1.06	1	1.12	0.05				
CD3+ T-cells *	1.07	1.01	1.15	0.03				
CD3+ CD4+ T-helper cells *	1.2	1	1.43	0.05	1.02	0.81	1.29	0.85
CD3+ CD8+ T-cytotoxic cells*	1.06	0.98	1.14	0.16				
CD3+ HLA-DR+ Activated T-cells*	1.39	1.12	1.72	0	1.41	1.09	1.83	**0.01**
CD16+ CD56+ CD3- Natural killer cells*	1.06	0.84	1.34	0.61				
CD19+ B-cells*	1.18	0.9	1.55	0.24	1.2	0.81	1.79	0.37
C-reactive protein*, per 10 mg/l higher	0.85	0.49	1.48	0.57	0.58	0.26	1.32	0.2
Number of ART switches since baseline	1.22	0.91	1.64	0.18	1.49	0.97	2.27	0.07
Hepatitis C co-infection	1	0.25	4	1				
HAART initiation 2001-2006 (vs. Before 2001)	0.3	0.13	0.68	0	0.71	0.27	1.9	0.49
HAART initiation 2007-2010 (vs. Before 2001)	0.23	0.08	0.69	0.01	0.42	0.07	2.41	0.33
Current PI regimen (vs. current NNRTI regimen)	2.25	1.08	4.69	0.03	1.56	0.61	3.99	0.35
Current PI+NNRTI regimen (vs. current NNRTI regimen)	3.16	1.1	9.08	0.03	1.44	0.37	5.58	0.6
Other regimen (vs. current NNRTI regimen)	1.17	0.3	4.66	0.82	0.5	0.07	3.79	0.51
Plasma drug levels subtherapeutic (vs. therapeutic)	0.62	0.2	1.97	0.42	0.52	0.12	2.26	0.38
Plasma drug levels missing (vs. therapeutic)	1.69	0.79	3.6	0.18	0.94	0.28	3.18	0.93
Time on HAART (per year)	1.53	1.13	2.08	0.01	1.47	1.04	2.06	0.03

Table 2: Determinants of viral blips in cases vs. controls (conditional logistic regression). *domain average area under the curve, per 100 cells/mmc higher

Subtherapeutic drug levels at index date were found in 6/23 (26.1%) cases and 12/34 (35.3%) controls (p = 0.46)

Limitations

- Activation markers were not assessed on CD4 and CD8 cells separately
- Plasma drug levels only assessed on a subset of patients
- Clinical endpoints not investigated here

Conclusion

- Higher levels of activated T-lymphocytes (CD3+HLA-DR+) in patients who developed a blip
- No such association found regarding C-reactive protein and other cellular markers including CD4 and CD8
- Blips not explained by lack of adherence
- Viral blips could help to identify patients with higher levels of immune activation and potentially higher risk for disease progression

References:
1. Garcia-Gasco P, Maida I, Blanco F, Barreiro P, Martin-Carbonero L, et al. (2008) Episodes of low level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome. Journal of Antimicrobial Chemotherapy 61: 699-704.
2. Nettles RE (2005) Intermittent HIV-1 Viremia (Blips) and Drug Resistance in Patients Receiving HAART. JAMA: The Journal of the American Medical Association 293: 817-829.
3. Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, et al. (2011) T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. J Infect Dis 203: 452-463.

Corresponding author:
Prof. Jan van Lunzen, MD, University Medical Center Hamburg-Eppendorf, Department of Medicine I/Infectious Diseases Unit, v.lunzen@uke.de, Phone: 004940741053964

Presented at IAS 2013 – Kuala Lumpur, Malaysia