

Silvia Nozza¹, Laura Galli¹, Nicola Gianotti¹, Nadia Galizzi^{1,2}, Andrea Poli¹, Paola Cinque¹, Vincenzo Spagnuolo^{1,2}, Adriano Lazzarin¹, Giuseppe Tambussi¹, Antonella Castagna^{1,2}.

1 Infectious Diseases Department, San Raffaele Scientific Institute, Milan, Italy. 2 Università Vita Salute San Raffaele, Milano, Italy.

Corresponding author: Silvia Nozza nozza.silvia@hsr.it

Background and aim of the study

Many markers of HIV reservoirs have been proposed, each one having a different meaning¹. HIVDNA allows to estimate the size of HIV reservoir². Objectives of the study were to determine prevalence of undetectable HIVDNA and to identify factors associated with this in a cohort of HIV-1 infected patients (pts) treated with antiretroviral therapy (ART) and with undetectable viral load (VL).

Methods

Cross-sectional study on HIV-1 infected pts followed at the Department of Infectious Diseases of San Raffaele Scientific Institute on stable ART, with availability of previous ART HIVRNA and with undetectable VL since ≥ 12 months. HIV-DNA was amplified and quantified by real-time PCR (ABI Prism 7900); limit of detectability is 100 copies/ 10^6 PBMC. Pts who were tested for HIV-RNA, HIV-DNA and immunological profile (CD4, CD8) at the same time were considered in the analysis. Results were described by median(IQR) or frequency(%). Logistic regression was used to identify predictive factors for HIVDNA <100 copies/ 10^6 PBMC.

Results

468 pts considered in the analyses, 119 (25%) with HIVDNA <100 copies/ 10^6 PBMC. Patients' characteristics at HIVDNA determination are summarized in Table 1.

At multivariate analysis, we found that pts with lower pre-ART HIVRNA [adjusted odds ratio (AOR) per \log_{10} cps/mL higher=0.68, 95%CI=0.51-0.90, $p=0.007$], higher nadir CD4 [AOR per 50-cells/ μ L higher=1.10, 95%CI=1.003-1.20, $p=0.046$] and a shorter time to ART start [AOR per 6-months higher=0.96, 95%CI=0.93-0.99, $p=0.019$] were more likely to have HIVDNA <100 copies/ 10^6 PBMC, after adjustment for age, gender, calendar year of ART start, type of current ART regimen, time on undetectable VL since ART start, current CD4 and CD4/CD8 ratio (Table 2). Prevalence of HIVDNA <100 copies/ 10^6 PBMC according to these factors is shown in Figure 1.

Figure 2 shows the percentage of patients with HIVDNA <100 copies/ 10^6 PBMC according to median nadir CD4, pre-ART HIVRNA and time to start ART.

Figure 1: Prevalence of HIVDNA <100 copies/ 10^6 PBMC according to CD4, pre-ART HIVRNA and months to start ART.

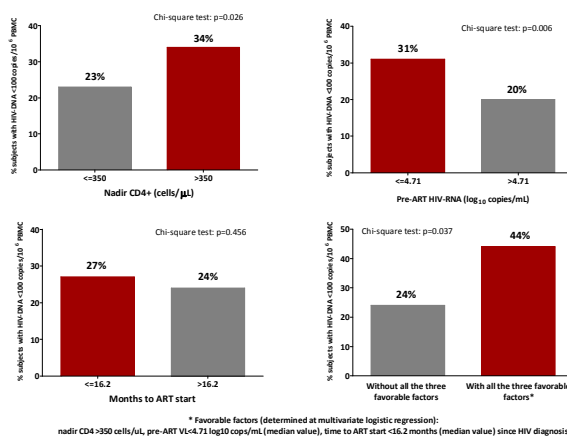


Figure 2: Percentage of patients with HIVDNA <100 copies/ 10^6 PBMC according to median nadir CD4, pre-ART HIVRNA and time to start ART.

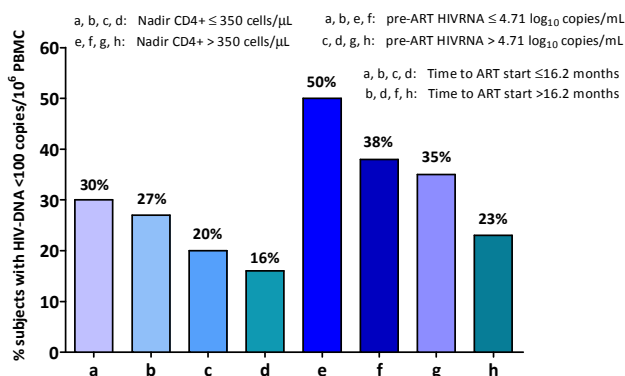


Table 1 Baseline patients' characteristics.

	HIV-DNA \geq 100 copies/ 10^6 PBMC (n=349)	HIV-DNA <100 copies/ 10^6 PBMC (n=119)	P-value
Male gender	81.7%	82.4%	0.999
Age (years)	37.9 (32.4-43.9)	36.6 (29.7-46.6)	0.400
Years of HIV infection	12 (7.21-18)	8.2 (4.6-13.3)	<0.0001
Years of ART	8.8 (4.5-14.2)	5.5 (3.1-10.4)	0.0001
AIDS diagnosis	49 (14%)	10 (8.4%)	0.149
CD4 nadir (cells/ μ L)	253 (154-337)	280 (204-388)	0.017
\leq 350 cells/ μ L	274 (78.5%)	81 (68.1%)	0.025
\leq 200 cells/ μ L	125 (35.8%)	28 (23.5%)	0.017
HIV risk factor			0.265
Man who have Sex with Men	89 (25.5%)	48 (40.3%)	
Heterosexual	29 (8.3%)	36 (30.3%)	
Intravenous Drug User	63 (18.1%)	7 (5.9%)	
HCVAb positive test	75 (21.5%)	17 (14.3%)	<0.0001
Previous HBsAg positive test	18 (5.2%)	7 (5.9%)	<0.0001
ART regimens			0.345
NRTI	11 (3.2%)	2 (1.7%)	
NNRTI	97 (28.3%)	31 (26.5%)	
PI	155 (45.2%)	63 (53.9%)	
INSTI	80 (23.3%)	21 (18%)	
HIV-RNA pre-ART (\log_{10} copies/mL)	4.78 (4.27-5.2)	4.51 (3.72-5.02)	0.002
Years HIV-RNA <50 copies/mL	4.34 (1.79-9.22)	3.58 (1.45-5.32)	0.004
%time with HIV-RNA <50 copies/mL since ART start	88.2 (73.35 - 94.63)	90.08 (75.92 - 95.77)	0.244
CD4 (cells/ μ L)			
>500 cells/ μ L	739 (557-932)	682 (491-897)	0.172
>276 cells/ μ L	276 (79.3%)	89 (74.8%)	0.306
CD4/CD8 ratio			
>1	0.91 (0.58-1.22)	0.87 (0.62-1.26)	0.779
>1	131 (41.1%)	44 (37.6%)	0.582

Table 2: Multivariate analysis on the risk of having HIVDNA <100 copies/ 10^6 PBMC.

Characteristics at HIV-DNA determination	Adjusted Odds Ratio (95% CI)	p-value
Age (per 5-years old)	0.981 (0.876-1.096)	0.739
Gender Female vs Male	0.983 (0.515-1.928)	0.960
Calendar year of ART start (per 2-years longer)	1.078 (0.972-1.197)	0.157
Months to ART (per 6-months longer)	0.963 (0.931-0.992)	0.019
ART regimens [§]		0.393
NNRTI vs PI	0.824 (0.472-1.421)	0.965
INSTI vs PI	0.663 (0.355-1.201)	0.294
%time HIVRNA <50 copies/mL since ART start (per 10% longer)	1.026 (0.900-1.175)	0.580
Nadir CD4 (per 50 cells/ μ L higher)	1.096 (1.003-1.201)	0.046
CD4 (per 50 cells/ μ L higher)	0.963 (0.914-1.011)	0.139
CD4/CD8 ratio (per 0.2-point higher)	1.004 (0.897-1.119)	0.938
Pre-ART HIV-RNA (per 1 \log_{10} copies/mL-higher)	0.675 (0.506-0.895)	0.007

[§] NRTI group was excluded.

Conclusions

In our chronic HIV infected pts, undetectable from 4 years, frequency of undetectable viral load is 25%. Lower pre-ART HIVRNA, shorter time between HIV diagnosis and starting ART and higher CD4 nadir were associated with undetectable HIVDNA. These findings may inform about selection of patients candidate to structured therapy interruption.

References

- Prevedel A et al. Identification, localization and Quantification of HIV reservoirs using microscopy Curr Protoc Cell Biol. 2018 Sep 28:e64
- Rouzioux C et al. HIV DNA: a clinical marker of HIV reservoirs. Curr Opin HIV AIDS 2018 Sep;13(5):389-394

Acknowledgments

We thank Gilead Sciences for an unrestricted grant to the CSLHIV Cohort of the Infectious Diseases Department, San Raffaele Hospital, Milan, Italy. The study was supported by Gilead Fellowship Program 2015.