Dettaglio abstract

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Title: PLWH with advanced HIV disease are at higher risk for becoming difficult to treat: data from a large cohort of PLWH starting modern ART regimens

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Authors: R. Gagliardini[1], A. Cozzi-Lepri[2], A. Tavelli[3], S. Rusconi [4,5], V. Spagnuolo[6], A. Giacomelli[7], G. Burastero[8], C. Agrati[1], M.M. Santoro[9], G. Madeddu[10], A. d'Arminio Monforte[11], A. Antinori[1]

Affiliation: [1]INMI Lazzaro Spallanzani IRCCS, Rome, Italy, [2]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL, [3]Icona Foundation, Milan, Italy, [4]Unità Operativa Malattie Infettive, Ospedale Civile di Legnano, Legnano, Italy, [5]Dipartimento di Scienze Biomediche e Cliniche “Luigi Sacco” Università degli Studi di Milano, Milan, Italy, [6]IRCCS San Raffaele Scientific Institute, Infectious Diseases Unit, Milan, Italy, [7]III Infectious Diseases Unit, ASST Fatebenefratelli Sacco, Ospedale Luigi Sacco, Milan, Italy, [8]Infectious Disease Clinic, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy, [9]University of Rome Tor Vergata, Department of Experimental Medicine, Rome, Italy, [10]Infectious Diseases Department of Medical, Surgical, and Experimental SciencesUniversity of Sassari, Italy
[11]University of Milan, Department of Health Sciences, Milan, Italy

Abstract
Background: Discontinuation of ART due to simplification, toxicities/intolerance and, less frequently, virological failure (VF), may potentially limit future ART options. Data which describe the characteristics and incidence rate of treatment failure of PLWH initiating modern ART are scarce.
Methods: All PLWH of the ICONA Foundation Study cohort who started a modern first-line ART (2NRTI + DRV/b; 2NRTI+ INSTI; 2NRTI+ RPV; 2NRTI+ DOR; DTG+3TC) were included. They were classified as “difficult to treat” (DTT) if, after starting ART, experienced ≥1 of the following events: i) ≥2 VF (VF defined as 2 consecutive viral load, VL>50 copies/mL) followed by ART change; ii) ≥2 treatment discontinuations due to toxicity/intolerance/failure on 2 different regimens; iii) ≥1 VF followed by ART change plus ≥1 treatment discontinuation due to toxicity/intolerance/failure. Comparison according to stage of HIV disease at ART initiation and outcome were performed by chi-square test for categorical and non-parametric Mann-Whitney test for continuous variables. Time to first fulfilling the DTT definition was estimated using the Kaplan-Meier (KM) method. Weighted and standard unweighted survival analysis by KM curves and Cox regression model were employed. The model was controlled for age, VL at ART starting, calendar year of ART and nationality.
Results: Among 8,061 PLWH included, 320 (4%) experienced one of the DTT-defining events (75% had ≥2 discontinuations, 18% had ≥1 VF + ≥1 discontinuation, 7% had ≥2 VF). DTT PLWH had a significantly higher prevalence of AIDS diagnosis, were slightly older, had lower CD4 cells count at nadir, had greater VL at ART starting, when compared to the non-DTT PLWH (Table 1). PLWH with advanced HIV disease (CD4<200 and/or AIDS) were 2,402 (30%) were more frequently females, infected through heterosexual contacts, not Italians, older and had greater viral load than PLWH without advanced HIV disease. Overall KM probabilities of becoming DTT were 9.95% (8.50-11.41%) by 8 years, with a significantly higher probability for PLWH with advanced HIV disease at unweighted (13.66% vs 8.55% p<0.0001) and weighted analysis (p=0.0426) (Figure 1). PLWH with advanced HIV disease had higher adjusted hazard rate of becoming DTT (aHR=1.30, 95% CI 0.98-1.74, p=0.072) when compared to PLWH without advanced HIV. ART started after fulfilling DTT definition was PI-based (±1-2 NRTI) in 16% of PLWH, INSTI-based in 56%, NNRTI-based in 13%, with ≥2 anchor drugs in 12%, with other drugs in 2% of them.
Conclusions: The probability of satisfying the definition of DTT after starting modern ART was of 9.95% by 8 years; PLWH with advanced HIV disease at ART initiation were at significantly higher risk of becoming DTT after controlling for confounding factors. Most PLWH after satisfying the DTT definition

started a regimen with 1 anchor drug + 1-2 NRTI, mainly INSTI-based, but more complex regimens were prescribed in 12% of cases indicating potential lack of therapeutic options.

Table 1: Main characteristics at enrolment by difficult to treat group

Characteristics	Difficult to treat			
	Yes N= 320	**No** N= 7741	**p-value**	**Total** N= 8061
Gender, n(%)			0.709	
Female	61 (19.1%)	1412 (18.2%)		1473 (18.3%)
Mode of HIV Transmission, n(%)			0.075	
IDU	22 (6.9%)	464 (6.1%)		486 (6.1%)
Homosexual contacts	137 (43.2%)	3774 (49.4%)		3911 (49.2%)
Heterosexual contacts	141 (44.1%)	2895 (37.4%)		3036 (37.7%)
Other/Unknown	17 (5.4%)	503 (6.6%)		520 (6.5%)
Nationality, n(%)			<.001	
Not Italian	97 (30.3%)	4171 (53.9%)		4268 (52.9%)
AIDS diagnosis, n(%)			<.001	
Yes	55 (17.2%)	763 (9.9%)		818 (10.1%)
HBsAg, n(%)			0.824	
Negative	254 (79.4%)	6177 (79.8%)		6431 (79.8%)
Positive	1 (0.3%)	13 (0.2%)		14 (0.2%)
Not tested	65 (20.3%)	1551 (20.0%)		1616 (20.0%)
HCVAb, n(%)			0.002	
Negative	230 (71.9%)	5774 (74.6%)		6004 (74.5%)
Positive	33 (10.3%)	438 (5.7%)		471 (5.8%)
Not tested	57 (17.8%)	1529 (19.8%)		1586 (19.7%)
Calendar year of baseline			<.001	
Median (IQR)	2014 (2013, 2016)	2016 (2015, 2018)		2016 (2015, 2018)
2008-2012	76 (23.8%)	542 (7.0%)		618 (7.7%)
2012-2016	193 (60.3%)	3344 (43.2%)		3537 (43.9%)
2017+	51 (15.9%)	3855 (49.8%)		3906 (48.5%)
Age, years			<.001	
Median (IQR)	43 (36, 50)	39 (31, 49)		40 (31, 49)
CD4 count, cells/mmc			<.001	
Median (IQR)	305 (105, 473)	355 (167, 534)		353 (163, 532)
<=200 cells/mmc	111 (38.4%)	2057 (28.7%)	<.001	2168 (29.1%)
CD4 count nadir, cells/mmc			<.001	
Median (IQR)	285 (104, 453)	348 (164, 510)		346 (160, 508)
CD8 count, cells/mmc			0.493	
Median (IQR)	866 (503, 1237)	863 (587, 1241)		863 (581, 1240)
Viral load, log10 copies/mL			0.001	
Median (IQR)	4.93 (4.34, 5.42)	4.72 (4.11, 5.30)		4.73 (4.12, 5.31)
>100,000 copies/mL, n(%)	112 (46.5%)	2322 (37.1%)	0.003	2434 (37.4%)
Time from HIV diagnosis to date of starting ART, months			0.186	
Median (IQR)	1 (1, 12)	1 (1, 6)		1 (1, 6)
Anchor drug started, n(%)			<.001	
NNRTI (DOR,RPV)	37 (11.6%)	1469 (19.0%)		1506 (18.7%)
PI (DRV/r)	149 (46.6%)	1568 (20.3%)		1717 (21.3%)
INSTI (RAL, EVG, DTG, BIC)	134 (41.9%)	4704 (60.8%)		4838 (60.0%)

Figure 1: Weighted survival KM estimates of becoming difficult to treat stratified by advanced HIV disease