Dettaglio abstract

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Title: Clinical and virological outcomes of difficult to treat patients in a large cohort of PLWH starting modern ART regimens

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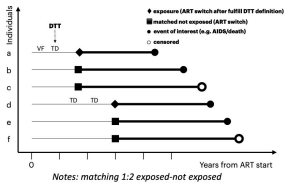
Abstract
Background: While virological failures (VF) rate in PLWH is declining, approximately 30% of PLWH discontinue 1st-line ART in recent years. Treatment failures to modern ART regimens are of concern, as they might limit future drug options and lead to clinical failure. Real world estimates of the rate of multiple failures to modern regimens are lacking and long-term consequences of these events remain unclear.
Methods: All participants of the ICONA Foundation Study cohort who started a modern first-line ART (2NRTI + DRV/b; 2NRTI + any INSTI; 2NRTI+ RPV; 2NRTI+ DOR; DTG+3TC) were included in this analysis. Patients 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. Time to fulfill DTT definition at its first occurrence (index date) was estimated using the Kaplan-Meier (KM) method. We then identified PLWH who, after the same time from starting ART, were still free from DTT events. In a subset of these who subsequently initiated a new regimen, we compared the treatment response between DTT (exposed) and matched unexposed (Figure 1) with respect to the following endpoints: a) VF b) discontinuation of ≥1 drug due to intolerance/toxicity/failure; c) treatment failure (composite of VL>200 cp/ml or b)) and d) clinical failure (AIDS/death, SNAE (Serious non-AIDS event)/death). Standard survival analysis by means of KM curves and Cox regression model were employed. The model was controlled for VL at ART, year of index date, nadir and current CD4 count fitted as time fixed covariate at index date.
Results: Among 8,061 PLWH included, 320 (4%) entered in the DTT definition. KM probabilities of becoming DTT were 2.2% (95% CI: 1.8-2.6%) by 2 years and 6.5% (5.8-7.4%) by 6 years.
In unadjusted analyses and compared to the matched unexposed group (matched analysis performed on 858 PLWH, Table 1), DTT showed higher probabilities of experiencing all the outcomes (Table 2). Associations were stronger for time to virological failure (p<0.0001), discontinuation of ≥1 drug due to intolerance/toxicity/failure (p=0.0001) and SNAE/death (p=0.003). After controlling for confounders, the association with the risk of discontinuation and time to AIDS/death was no longer significant. In contrast, for the associations remained significant after the adjustment (Figure 2).
Conclusion: A total of 6.5% of PLWH starting modern first-line ART satisfied our arbitrary definition of

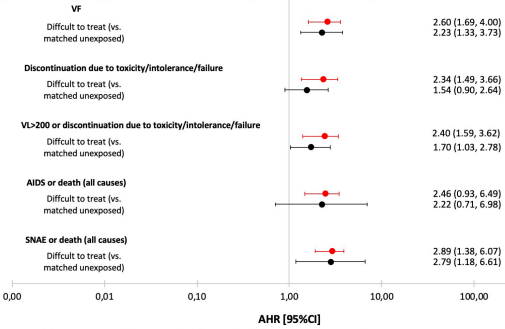
DTT by 6 years from ART initiation. This appears to be a more vulnerable PLWH population who in the long-term experiences higher risk of treatment and clinical failures. PLWH showing early signs of DTT events should be carefully managed to prevent morbidity and mortality.

Figure 1: Schematization of the matching process



Notes: matching 1:2 exposed-not exposed

Figure 2: Cox regression model for VF, discontinuation, treatment failure or clinical failure



Notes: unadjusted analyses in red, adjusted analyses in black. SNAE, Serious non-AIDS event; AHR, adjusted hazard rate.

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

	Difficult to treat			
Characteristics	Yes	No	p-value*	Total
	N= 286	N= 572		N= 858
Gender, n(%)			0.404	
Female	53 (18.5%)	93 (16.3%)		146 (17.0%)
Mode of HIV Transmission, n(%)			0.487	
IDU	18 (6.4%)	35 (6.2%)		53 (6.2%)
Homosexual contacts	129 (45.6%)	289 (50.9%)		418 (49.1%)
Heterosexual contacts	120 (42.0%)	211 (36.9%)		331 (38.6%)
Other/Unknown	16 (5.7%)	33 (5.8%)		49 (5.8%)
Nationality, n(%)			0.747	
Not Italian	78 (27.3%)	162 (28.3%)		240 (28.0%)
AIDS diagnosis, n(%)			0.001	
Yes	69 (24.1%)	87 (15.2%)		156 (18.2%)
HBsAg, n(%)			0.348	
Negative	254 (88.8%)	489 (85.5%)		743 (86.6%)
Positive	2 (0.7%)	8 (1.4%)		10 (1.2%)
Not tested	30 (10.5%)	75 (13.1%)		105 (12.2%)
HCVAb, n(%)			0.043	
Negative	234 (81.8%)	475 (83.0%)		709 (82.6%)
Positive	29 (10.1%)	34 (5.9%)		63 (7.3%)
Not tested	23 (8.0%)	63 (11.0%)		86 (10.0%)
Calendar year of baseline**			<.001	
Median (IQR)	2017 (2016, 2019)	2018 (2017, 2019)		2018 (2017, 2019)
2008-2012	15 (5.2%)	8 (1.4%)		23 (2.7%)
2012-2016	82 (28.7%)	96 (16.8%)		178 (20.7%)
2017+	189 (66.1%)	468 (81.8%)		657 (76.6%)
Age, years			<.001	
Median (IQR)	47 (39, 54)	43 (35, 52)		44 (37, 52)
CD4 count, cells/mmc			0.089	
Median (IQR)	571 (302, 823)	606 (406, 841)		597 (379, 838)
<=200 cells/mmc	34 (12.0%)	48 (8.4%)	0.094	82 (9.6%)
CD4 count nadir, cells/mmc			0.022	
Median (IQR)	260 (81, 425)	303 (122, 458)		290 (109, 453)
CD8 count, cells/mmc			0.415	
Median (IQR)	859 (617, 1188)	842 (612, 1123)		848 (613, 1146)
Viral load, log10 copies/mL			<.001	
Median (IQR)	1.38 (0.00, 1.81)	1.30 (0.00, 1.59)		1.30 (0.00, 1.60)
>100,000 copies/mL, n(%)	16 (5.7%)	11 (1.9%)	0.003	27 (3.2%)
Time from HIV diagnosis to index date, months			0.585	
Median (IQR)	41 (20, 71)	43 (21, 75)		42 (20, 75)
Anchor drug started, n(%)			0.049	
NNRTI (DOR, RPV)	45 (15.7%)	140 (24.5%)		185 (21.6%)
PI (DRV/r)	61 (21.3%)	96 (16.8%)		157 (18.3%)
INSTI (RAL, EVG, DTG, BIC)	187 (65.4%)	349 (61.0%)		536 (62.5%)

Table 2. KM estimates (with 95% CI) by outcome and exposure groups

	2-year	4-year	6-year
	VF (log-rank p<0.0001)		
Matched unexposed	7.2% (5.1-10.1)	8.9% (5.9-12.0)	-
DTT	17.8% (12.9-22.7)	20.9% (15.3-26.5)	-
	Discontinuation due to failure/intolerance/toxicity (log-rank p=0.0001)		
Matched unexposed	6.2% (4.1-9.2)	14.8% (8.9-20.7)	-
DTT	17.0% (11.7-22.4)	22.6% (15.7-29.5)	-
	Treatment failure (log-rank p<0.0001)		
Matched unexposed	7.7% (5.1-10.4)	16.2% (10.3-22.2)	-
DTT	19.1% (13.7-24.5)	25.8% (18.6-32.9)	-
	AIDS/death (log-rank p=0.06)		
Matched unexposed	0.9% (0.1-1.76)	1.5% (0.1-2.8)	
DTT	3.3% (1.0-5.6)	4.1% (1.3-6.8)	10.1% (0-21.8)
	SNAE/death (log-rank p=0.003)		
Matched unexposed	1.3% (0.3-2.4)	2.8% (0.8-4.7)	6.8% (0.4-13.2)
DTT	4.6% (1.9-7.2)	7.9% (4.0-11.8)	17.0% (5.3-28.6)

Notes: DTT, difficult to treat; SNAE, Serious non-AIDS event.