Durability of Different Initial Regimens in Patients Starting ART with CD4+ Counts <200 cells/μL and HIV-RNA >5 log_{10} copies/mL.

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BACKGROUND

Late HIV diagnosis is still frequent, leading often to antiretroviral therapy (ART) start with very low CD4+ counts, high viral load and an active opportunistic disease. Nevertheless, patients with active opportunistic diseases, or with less than 200 CD4+ cells/μL and more than 5 log_{10} HIV-RNA copies/mL, at ART start are largely underrepresented in clinical trials; data from large observational studies may help bridging this knowledge gap.

STUDY OBJECTIVES

To study the durability of different initial regimens in patients starting ART with CD4+ counts <200 cells/μL and HIV-RNA >5 log_{10} copies/mL.

MATERIAL AND METHODS

ICONA Foundation Study is a multi-center prospective observational study of HIV-1-infected patients, which was set up in 1997. Eligible patients are those starting ART when they are naive to antiretrovirals, regardless of the reason for which they had never been previously treated and of the stage of their disease. The ICONA Foundation study has been approved by IRB of all the participating centers; sensitive data from patients are seen only in aggregate form. All patients sign a consent form to participate in ICONA, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amendment October 2013). Demographic, clinical and laboratory data and information on therapy are collected for all participants and recorded using electronic data collection [www.icona.org].

Patients are followed-up prospectively at each of the clinical sites participating in the study and HIV viral load monitoring in cohort participants is performed at least twice yearly, according to study protocol and to Italian guidelines. Dates of start and stop of each antiretroviral are collected together with the main reason for discontinuing as reported by the treating physician.

The database for the analysis has been put together retrospectively selecting only subjects who started ART with 1 anchor drug (ritonavir or cobicistat-boosted protease inhibitor [bPI], or non-nucleoside reverse transcriptase inhibitor [NNRTI] or integrase strand transfer inhibitor [InSTI]) plus tenofovir (TDF)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC), CD4+ <200 cells/μL and HIV-RNA >5 log_{10} copies/mL, and at least 1 HIV-RNA assessed both before and after the start of ART, were included in this analysis.

Primary study endpoint was treatment failure (TF), defined as virological failure (VF, first of 2 consecutive HIV-RNA>50 copies/mL after>6 months of treatment) or discontinuation of class of the anchor drug. Cumulative probability of treatment failure according to drug class was assessed by Kaplan Meier method and compared by log-rank test. Independent associations were investigated by Poisson regression analysis, in a model including variables associated with TF at a p-value <.1 at univariate analysis: anchor drug, baseline HIV-RNA, CDC C stage, HCV co-infection, CD4+ cell count, FIB-4, eGRF, ongoing opportunistic disease, nucleos(t)ide backbone. Secondary study endpoints were the cumulative probability of TF in the stratum of patients starting ART with >500,000 HIV-RNA copies/mL, the cumulative probability of VF and changes in CD4+ cell counts during follow-up.

DISCUSSION

In patients with very advanced HIV infection, the type of regimen was independently associated with treatment failure; this result is in line with those from secondary analyses of randomized controlled trials

- InSTI more effective than bPIs in high baseline viral load strata
- Better tolerability of InSTIs compared to NNRTIs and particularly to bPIs

However, the association between type of initial regimen and treatment failure was not confirmed when considering only patients starting ART with >500,000 HIV-RNA copies/mL.

The only other factor independently associated with treatment failure was the viral load before ART start.

A viral load before ART start >500,000 HIV-RNA copies/mL was also independently and directly associated to virological failure. By contrast, the type of initial regimens was not independently associates with virological failure.

CD4+ cells gain during follow-up was optimal with any regimen and comparable among types of regimen.

The main limitation of this study was the lack of randomization; however, although statistically significant, baseline differences between groups were not clinically relevant.

CONCLUSIONS

In patients starting ART with <200 CD4+ cells/μL and >5 log_{10} HIV-RNA copies/mL, the durability of regimens based on NNRTIs (EFV in 95% of cases) or InSTIs was longer than that of bPI-based regimens.

RESULTS

1127 patients fulfilled the inclusion criteria: 729 started ART with a bPI (349 [48%] DRV/r, 210 [29%] ATV/r, 150 [21%] ATV/r, 15 [2%] FPV/r, 5 [<1%] DRV/c), 305 with an InSTI (147 [48%] DTG, 87 [29%] EVG, 71 [23%] RAL) and 193 with a NNRTI (182 [94%] EFV, 5 [3%] RPV, 4 [2%] NVP, 2 [1%] ETV).

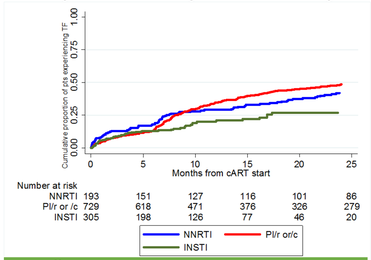
Table 1. Baseline characteristics.

	Overall N=1227	NNRTI N=193	bPI N=729	InSTI N=305	*p-value*
Male gender, n(%)	926 (75.5%)	151 (78.2%)	546 (74.9%)	229 (75.1%)	0.621
Age, median (IQR)	42 (35-51)	41 (33-50)	42 (35-50)	44 (36-53)	0.004
Mode of HIV transmission					0.008
heterosexual	663 (54.0%)	110 (57.0%)	402 (55.1%)	151 (49.5%)	
IVDU	83 (6.8%)	16 (8.3%)	56 (7.7%)	11 (3.6%)	
MSM	350 (28.5%)	48 (24.9%)	205 (28.1%)	97 (31.8%)	
Other/unknown	131 (10.7%)	19 (9.8%)	66 (9.1%)	46 (15.1%)	
CDC stage C	450 (36.7%)	70 (36.3%)	262 (35.9%)	118 (38.7%)	0.699
HCV co-infection					<0.001
negative	917 (74.7%)	141 (73.1%)	553 (75.9%)	223 (73.1%)	
positive	95 (7.7%)	26 (13.5%)	59 (8.1%)	10 (3.3%)	
not known	215 (17.5%)	26 (13.5%)	117 (16.1%)	72 (23.6%)	
HBV co-infection					0.216
negative	951 (77.5%)	153 (79.3%)	569 (78.1%)	229 (75.1%)	
positive	61 (5.0%)	13 (6.7%)	36 (4.9%)	12 (3.9%)	
not known	215 (17.5%)	27 (14.0%)	124 (17.0%)	64 (21.0%)	
CD4+ cells/μL, median (IQR)	63 (27-125)	94 (32-147)	60 (23-121)	60 (29-112)	<0.001
CD4+ cells/μL, n (%)					<0.001
0-100	808 (68.9%)	101 (52.3%)	494 (67.8%)	213 (69.8%)	
101-200	419 (34.2%)	92 (47.7%)	235 (32.2%)	92 (30.2%)	
CD4+/CD8+ ratio					0.374
<0.30	736 (60%)	108 (56.0%)	447 (61.3%)	181 (59.3%)	
0.30-0.45	57 (4.6%)	13 (6.7%)	30 (4.1%)	14 (4.6%)	
>0.45	34 (2.8%)	8 (4.1%)	15 (2.1%)	11 (3.6%)	
missing	400 (32.6%)	64 (33.2%)	237 (32.5%)	99 (32.5%)	
CD4+/CD8+ ratio, median (IQR)	0.11 (0.05-0.20)	0.14 (0.08-0.24)	0.11 (0.05-0.19)	0.10 (0.06-0.19)	0.005
HIV RNA copies/mL, n (%)					0.092
100,000-500,0000	788 (64.2%)	135 (69.9%)	469 (64.3%)	184 (60.3%)	
>500,000	439 (35.8%)	58 (30.1%)	260 (35.7%)	121 (39.7%)	
HIV-RNA (log_{10} copies/mL)	5.55 (5.30-5.87)	5.49 (5.24-5.80)	5.57 (531-5.88)	5.55 (5.30-5.88)	0.150
FIB4 score					0.707
<1.45	608 (49.5%)	99 (51.3%)	368 (50.5%)	141 (46.2%)	
1.45-3.25	334 (27.2%)	51 (26.4%)	193 (26.5%)	90 (29.5%)	
>3.25	109 (8.9%)	20 (10.4%)	64 (8.8%)	25 (8.2%)	
missing	176 (14.3%)	23 (11.9%)	104 (14.3%)	49 (16.1%)	
eGFR (CKD EPI), min/ml/1.73m²					0.844
≤60	1069 (87.1%)	172 (89.1%)	630 (86.4%)	267 (87.5%)	
>60	30 (2.4%)	4 (2.1%)	20 (2.7%)	6 (2.0%)	
missing	128 (10.4%)	17 (8.8%)	79 (10.8%)	32 (10.5%)	
Ongoing opportunistic disease	424 (34.6%)	65 (33.7%)	247 (33.9%)	112 (36.7%)	0.656
Haemoglobin					0.197
<12 (F) OR <14 (M) g/dL	887 (72.3%)	131 (67.9%)	524 (71.9%)	232 (76.1%)	
≥12 (F) OR ≥14 (M) g/dL	270 (22.0%)	53 (27.5%)	160 (22.0%)	57 (18.7%)	
missing	70 (5.7%)	9 (4.7%)	45 (6.2%)	16 (5.2%)	
Hb g/dL, median (IQR)	12.1 (10.6-13.4)	12.4 (10.8-13.8)	12.2 (10.7-13.4)	11.8 (10.3-13.3)	0.015
Platelets					0.493
normal (150,000-450,000)	721 (58.8%)	116 (60.1%)	421 (57.7%)	184 (60.3%)	
<150,000 or >450,000	420 (34.2%)	67 (34.7%)	258 (35.4%)	95 (31.1%)	
missing	86 (7.0%)	10 (5.2%)	50 (6.9%)	26 (8.5%)	
Platelets, x10³, median (IQR)	176 (132-233)	181 (133-225)	175 (131-234)	177 (134-236)	0.736
Neutrophils					0.004
normal (2.000-7.000)	549 (4.7%)	96 (49.7%)	328 (45.0%)	125 (41.0%)	
<2.000 or >7.000	516 (42.1%)	84 (43.5%)	309 (42.4%)	123 (40.3%)	
missing	162 (13.2%)	13 (6.7%)	92 (12.6%)	57 (18.7%)	
Year of cART start					<0.001
2004-2006	27 (2.2%)	6 (3.1%)	21 (2.9%)	0 (0%)	
2007-2009	148 (12.1%)	33 (17.1%)	114 (15.6%)	1 (0.3%)	
2010-2012	406 (33.1%)	101 (52.3%)	294 (40.3%)	11 (3.6%)	
2013-2015	435 (35.4%)	51 (26.4%)	259 (35.5%)	125 (41.0%)	
2016-2017	211 (17.2%)	2 (1.0%)	41 (5.6%)	168 (55.1%)	
NRTI combination					<0.001
FTC+TDF	1097 (89.4%)	189 (97.9%)	666 (91.4%)	242 (79.3%)	
ABC+3TC	130 (10.6%)	4 (2.1%)	63 (8.6%)	63 (20.7%)	

Table 2. Main outcomes.

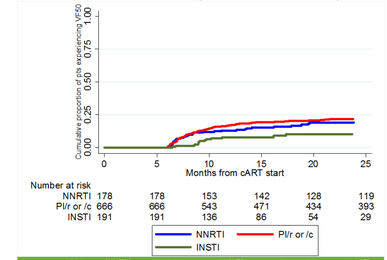
	Overall	NNRTI	bPI	InSTI
PYFU	2316	519	1533	264
Treatment failure, n (%)	595 (48.5%)	94 (48.7%)	446 (61.2%)	55 (18.0%)
IR (95%CI) per 100 PYFU	25.7 (23.7-27.8)	18.1 (14.8-22.2)	29.1 (26.5-31.9)	20.8 (26.5-31.9)
	Overall	NNRTI	bPI	InSTI
PYFU	3069	672	2125	272
virological failure, n (%)	225 (18.3%)	40 (22.5%)	171 (25.7%)	14 (7.3%)
IR (95%CI) per 100 PYFU	7.3 (6.4-8.4)	5.9 (4.4-8.1)	8.0 (6.9-9.3)	5.2 (3.1-8.7)

Figure 1. Cumulative probability of TF according to the anchor drug of the initial ART regimen.



	No. With TF	PYFU	1-year probability	95%CI	2-year probability	95%CI
NNRTI	94	519	29.1%	23.1-36.2	41.9%	35.0-49.6
bPI	446	1533	34.7%	31.3-38.4	48.8%	45.0-52.7
INSTI	55	264	21.0%	16.1-27.2	26.7%	20.4-34.5

Figure 2. Cumulative probability of VF according to the anchor drug of the initial ART regimen.



	No. with VF	PYFU	1-year probability	95%CI	2-year probability	95%CI
NNRTI	40	672	13.0%	8.9-19.0	19.1%	14.0-25.8
bPI	171	2125	17.1%	14.4-20.2	21.8%	18.7-25.2
INSTI	14	272	7.8%	4.5-13.3	10.2%	6.0-17.0

Figure 3. Median CD4+ cell counts at selected time-points during follow-up, according to the initial ART regimen.

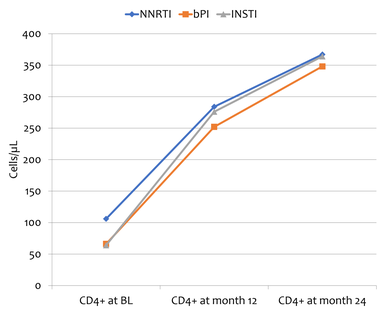


Table 3. Univariable and multivariable analysis of factors associated with TF. Multivariable models included variables retained from univariable because their p-value was <0.1.

	Unadjusted IRR (95% CI)	*p-value*	Adjusted IRR (95% CI)	*p-value*
Female vs male gender	1.10 (0.91-1.32)	0.322	-	
Age (10 yrs older)	1.05 (0.98-1.14)	0.170	*	
Age >45 yrs	1.26 (1.07-1.48)	0.006	*	
Mode of HIV transmission				
heterosexual	1.00		-	
IVDU	0.76 (0.54-1.07)	0.112		
homosexual	1.09 (0.91-1.31)	0.332	-	
Other/unknown	0.99 (0.75-1.32)	0.961	-	
CDC stage C	1.21 (1.03-1.43)	0.023	1.10 (0.61-1.97)	0.750
HCV co-infection				
negative	1.00		1.00	
positive	0.74 (0.55-1.01)	0.056	0.80 (0.59-1.09)	0.160
not known	0.89 (0.72-1.11)	0.308	0.93 (0.74-1.16)	0.511
HBV co-infection				
negative	1.00		-	
positive	0.91 (0.62-1.33)	0.615	-	
not known	1.01 (0.81-1.25)	0.944	-	
CD4+ cells/μL				
0-100	1.00		1.00	
101-200	0.77 (0.65-0.92)	0.003	0.90 (0.75-1.08)	0.274
CD4+/CD8+ ratio				
<0.3	1.00		-	
0.3-0.45	1.03 (0.70-1.51)	0.888	-	
>0.45	1.05 (0.65-1.71)	0.833	-	
missing	0.90 (0.75-1.07)	0.241	-	
HIV RNA copies/mL				
100,000-500,000	1.00		1.00	
>500,000	1.46 (1.24-1.72)	<0.001	1.37 (1.16-1.63)	<0.001
FIB4 score				
<1.45	1.00		1.00	
1.45-3.25	1.04 (0.87-1.26)	0.653	1.02 (0.84-1.24)	0.843
>3.25	1.02 (0.76-1.36)	0.901	1.02 (0.76-1.38)	0.882
missing	0.80 (0.62-1.04)	0.093	0.85 (0.59-1.25)	0.416
eGFR (CKD EPI), mL/min/1.73m²				
≤60	1.00		1.00	
>60	1.10 (0.67-1.82)	0.697	1.07 (0.65-1.78)	0.791
missing	0.75 (0.56-0.99)	0.041	0.75 (0.49-1.15)	0.190

* not included in the model because the variable "age" is already considered in the calculation of both the eGFR and the FIB4 score.

(continued)	Unadjusted IRR (95% CI)	*p-value*	Adjusted IRR (95% CI)	*p-value*
Ongoing opportunistic disease	1.21 (1.03-1.43)	0.024	1.07 (0.59-1.92)	0.825
Haemoglobin				
≥12(F) OR ≥14 (M) g/dL	1.00		1.00	
<12(F)OR <14 (M) g/dL	1.27 (1.04-1.55)	0.020	1.12 (0.91-1.38)	0.284
missing	0.98 (0.66-1.44)	0.914	1.33 (0.76-2.31)	0.317
Platelets				
normal (150.000-450.000)	1.00		-	
<150.000 or >450.000	1.02 (0.86-1.20)	0.856	-	
missing	0.84 (0.60-1.19)	0.327	-	
Neutrophils				
normal (2.000-7.000)	1.00		-	
<2.000 or >7.000	1.02 (0.86-1.21)	0.832	-	
missing	0.96 (0.74-1.25)	0.751	-	
Year of ART start				
2004-2006	0.92 (0.58-1.46)	0.721		
2007-2009	0.91 (0.73-1.14)	0.406		
2010-2012	1.00			
2013-2015	1.17 (0.97-1.41)	0.109		
2016-2017	1.22 (0.84-1.77)	0.293		
NRTI combination				
FTC+TDF	1.00		1.00	
ABC+3TC	1.26 (0.95-1.68)	0.109	1.19 (0.89-1.60)	0.231
Anchor drug class (alternative 1)				
NNRTI	1.00		1.00	
bPI	1.61 (1.29-2.01)	<0.001	1.54 (1.22-1.93)	<0.001
INSTI	1.15 (0.83-1.61)	0.407	1.07 (0.76-1.50)	0.704
Anchor drug class (alternative 2)				
NNRTI	0.62 (0.50-0.78)	<0.001	0.65 (0.52-0.82)	<0.001
bPI	1.00		1.00	
INSTI	0.72 (0.54-0.95)	0.019	0.69 (0.52-0.92)	0.012

Table 4. Effect of third drug class on treatment failure among the 439 patients who started ART with HIV-RNA >500,000 copies/mL.

	Unadjusted IRR (95%CI)	*p-value*	Adjusted IRR (95%CI)	*p-value*
NNRTI	0.61 (0.42-0.89)	0.010	0.69 (0.46-1.03)	0.067
bPI	1.00		1.00	
INSTI	0.91 (0.61-1.34)	0.630	0.98 (0.66-1.46)	0.918

Table 5. Multivariable analysis of factors independently associated with VF (includes only variables retained from univariable because their p-value was <0.1).

	Adjusted IRR (95%CI)	*p-value*
CD4+ cell/μL, n (%)		
0-100	1.00	
101-200	0.89 (0.67-1.20)	0.456
HIV-RNA copies/mL, n(%)		
100,000-500,000	1.00	
>500,000	1.71 (1.31-2.23)	<0.001
Haemoglobin		
≥12 (F) OR ≥14 (M) g/dL	1.00	
<12 (F)OR <14 (M) g/dL	1.26 (0.89-1.78)	0.190
missing	0.77 (0.37-1.59)	0.475

(continued)	Adjusted IRR (95%CI)	*p-value*
NRTI combination		
FTC+TDF	1.00	
ABC+3TC	1.07 (0.67-1.72)	0.777
Anchor drug class		
NNRTI	0.78 (0.55-1.11)	0.171
bPI	1.00	
INSTI	0.62 (0.36-1.07)	0.090

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