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Poster 602

Impact of Minority Drug Resistant and X4 variants in Naïve Patients Starting ART with <100 CD4+ T cells/mm^3

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Background

HIV-1-infected subjects initiating first-line antiretroviral therapy (ART) with CD4+ T cell counts <100 c/mm^3 are at increased risk for developing virological failure (VF), opportunistic diseases and death. The impact of drug-resistant minority variants (DRMV) and HIV-1 tropism on first-line ART outcomes remains unknown in these subjects.

Methods

We performed a *post hoc* analysis from 2 open-label, prospective, randomized clinical trials comparing the efficacy of first-line ART with efavirenz (EFV) vs. indinavir/ritonavir (IDV/r) + Combivir® (ADVANZ study), and EFV vs. atazanavir/ritonavir (ATV/r) vs. lopinavir/ritonavir (LPV/r) + Truvada® (ADVANZ-3 study). Subjects were ART-naïve, had CD4+ T cell counts <100 c/mm^3 and wildtype HIV-1 by bulk sequencing at study entry. Stored pre-ART samples were reanalysed for the presence of DRMVs and X4 HIV-1 using 454 sequencing. The detection threshold for DRMVs was 0.5%; X4 HIV-1 was defined as ≥1% variants with a Geno2Pheno$_{[coreceptor]}$ FPR ≤10%. Virological failure was defined as 2 consecutive VL≥200 c/mL or one VL≥1000 c/mL at or after month 6 of ART. The different study arms were combined in 2 groups: those starting EFV (EFV group) and those starting a PI/r regimen (PI/r group). Kaplan-Meier and univariate and multivariate Cox regression analyses were used to evaluate associations between baseline risk factors and VF.

Results

From 151 subjects, 3 were excluded because they did not have assigned treatment, 3 because they were lost to follow-up at baseline, and 4 because they had a GSS <3 from mutations found ≥20% **(Figure 1)**. This left 141 evaluable subjects; 57 received EFV and 84 PI/r therapy (28 ATV/r, 27 IDV/r and 29 LPV/r). Median (IQR) pre-ART CD4+ T cell counts and VL were 39 (20; 60) cells/mm^3 and 257,424 (66,400; 500,001) c/mm^3, respectively. 95 (67%) subjects had X4 HIV-1 **(Table 1)**. Mutations conferring a treatment-adjusted HIVdb score >0 were identified **(Table 2)**. Pre-existence of DRMV conferring an HIVdb score≥10 to the regimen initiated was associated with a significantly increased risk of VF in the Kaplan-Meier analysis including all subjects and those initiating EFV **(Figure 2a, 2b, 2c)**, whereas HIV-1 tropism was not **(Figure 2d)**. There were no differences in CD4 increases by baseline tropism or presence of DRMVs **(Figure 3)**. Factors associated (p<0.1) with VF in the univariate Cox analysis **(Table 3)** were HIVdb score ≥10, Age ≥35 years and ART group. The only variable that remained associated with VF in the mutivariate Cox regression model **(Table 4)**, was the baseline HIVdb score ≥10: Hazard Ratio (HR)=2.82 (95CI: 1.23-6.54), p=0.015, when considering all subjects; and HR=6.02 (95CI: 0.03-0.75), p=0.002, in those initiating EFV.

Conclusions

Pre-existing DRMVs decrease the antiviral efficacy of first-line ART including EFV in subjects with advanced immune deterioration at diagnosis. Ultrasensitive genotypic resistance testing may help improve ART outcomes in these subjects.

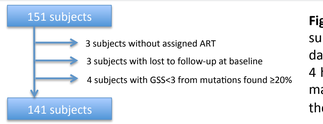


Figure 1: Subject disposition. From the initial 151 subjects, 3 did not have assigned treatment in the database, 3 were lost to follow-up at baseline, and 4 had GSS<3 due to the presence of drug-resistant majority variants >20% in viral population. All these subjects were excluded from the study.

Characteristics		Total	Virological Failure	No Virological Failure	p-value
Gender, n(%)	Men	112 (79%)	21	91	0.429
Age, median (IQR)	Years	39 (33, 47)	35	40.5 (34, 47)	0.065
HIV exposure group, n (%)	MSMs	60 (42.6%)	9	51	0.493
	Heterosexual	60 (42.6%)	15	45	
	IDU	12 (8.5%)	4	8	
	Heterosexual + IDU	3 (2.1%)	0	3	
	Bisexual	2 (1.4%)	0	2	
	Unknown	4 (2.8%)	1	3	
Treatment, n (%)	EFV	57 (40.4%)	7	50	0.193
	ATVr	28 (19.9%)	7	21	
	IDVr	27 (19.1%)	6	21	
	LPVr	29 (20.6%)	8	20	
HIV RNA, median (IQR)	copies/mm^3	257424 (66400, 500001)	330000 (58159, 671264)	235153 (66393, 500000)	0.277
CD4+ counts, median (IQR)	cells/mm^3	38.5	41 (21.5, 61)	37 (19, 60)	0.622
Tropism, n (%) (FPR 10%)	CCR5	44 (31%)	10	34	0.886
	CXCR4	95 (67%)	19	76	
	Non amplifiable	2 (1%)	0	2	
HBV coinfection, n (%)	Positive	12 (8.5%)	2	10	0.716
	Negative	127 (90.1%)	27	100	
	Unknown	2 (1.4%)	0	2	
HCV coinfection, n (%)	Positive	25 (17.7%)	6	19	0.877
	Negative	111 (78.8%)	22	89	
	Unknown	5 (3.5%)	1	4	

Table 1: Subject's characteristics at baseline. There were no statistically significant differences between subjects with or without virological failure.

Subject ID	Treatment arm	Treatment	Mutations found (%) Mutations impacting ART efficacy	Mutations with no impact in treatment	Treatment adjusted score
AD28	EFV	EFV,AZT,3TC	M184I (1.2)	A71V (99.8); V106I (1.4); I13V (3.4); M36I (6.0); I62V (26.8); L63P (99.5); I93L (99.9); T69S (10.7); L210M (23.7)	50
AD25	EFV	EFV,AZT,3TC	V179D (1.0)	L10I (1.0); V77I (77.3); I93L (85.3); K101R (6.5); L63P (100)	30
AD256	EFV	EFV,AZT,3TC	Y181C (0.8)	M36I (3.0); I64L (94.8); L63P (100)	30
AD2118	EFV	EFV,TDF,FTC	V179D (99.7); L210W (5.6)	T69S (2.5); V77I (100)	25
AD242	EFV	EFV,AZT,3TC	V179D (19.9); L10F (99.8)	M36I (7.4); V106I (0.6)	15
AD2126	EFV	EFV,TDF,FTC	V106I (1.4)	M36I (3.2); I62V (99.0); L63P (99.8); E44D (13.6)	10
AD2136	EFV	EFV,TDF,FTC	M41L (0.5)	N83D (1.6); D60E (98.6); T69S (1.3); V179I (0.8) M36I (100)	10
AD241	EFV	EFV,AZT,3TC	A98G (2.2); E138Q (36.5)	L10V (6.1); I64L (99.8); L63P (100)	10
AD229	EFV	EFV,AZT,3TC	V118I (99.7)		10
AD2127	EFV	EFV,TDF,FTC	V108I (30.3); K219Q (28.0)	A71T (99.1); M36I (99.2); I62V (64.3); L63P (35.5); I93L (99.9); K101R (14.9); D60E (100)	10
AD2149	EFV	EFV,TDF,FTC	V179D (22.4)	I50V (0.7); I13V (99.5); M36I (5.9); I64V (99.5); V77I (85.1)	10
AD273	EFV	EFV,TDF,FTC	E138G (5.9)	T69N (2.4); V179I (99.9)	5
AD233	EFV	EFV,AZT,3TC	T69N (100)	M36I (100); I62V (10.8); L63P (100); I64V (94.8)	5
AD253	EFV	EFV,AZT,3TC	T69N (30.5)	M36I (1.6); I62V (10.9); V77I (5.1); I13V (100); L63P (100)	5
AD237	IP	IDV/r,AZT,3TC	D67G (1.0); T69S (1.2); T69N (78.8); T215I (2.4)	M36I (92.9); I62V (0.7); I64V (24.7); V106I (73.1); V179D (15.5); L210S (0.7)	35
AD268	IP	ATV/r,TDF,FTC	V32I (0.8); M46I (0.5)	V77I (22.3); L63P (100)	25
AD27	IP	IDV/r,AZT,3TC	E44D (17.0); V118I (3.7)	L33I (44.2); L33V (54.9); K20R (2.2); M36I (0.5); L63P (99.3); I64L (0.7); I93L (99.3)	20
AD279	IP	LPV/r,TDF,FTC	M46I (0.8)	V106I (27.0); G16E (98.9); I64V (99.8); V77I (99.8)	10
AD296	IP	LPV/r,TDF,FTC	L10I (99.6)	I13V (99.7); L63P (99.5); T69I (0.7); A98S (0.7); V118I (0.7); D60E (100); I62V (100); I64V (100)	10
AD297	IP	ATV/r,TDF,FTC	M46I (12.2)	L63P (85.5); I64V (14.3); V77I (22.8); V82I (0.5); I93L (99.4); V106I (0.8)	10
AD2103	IP	ATV/r,TDF,FTC	G73S (1.2)	I13V (96.5); G16E (12.0); I62V (99.6); L63P (83.7); I64V (99.8); I85V (2.5); A98S (99.2); D60E (100); V77I (100)	10
AD2124	IP	LPV/r,TDF,FTC	L10I (99.9)	V118I (1.4); M36I (99.9); I93L (38.1)	10
AD2150	IP	ATV/r,TDF,FTC	M46I (0.6)	L33I (0.6); L33V (99.3); I62V (33.0); V75L (2.8); V106I (8.0); I64V (100)	10
AD231	IP	IDV/r,AZT,3TC	V118I (100)	L10V (); I13V (); K20R (); M36I (); L63P (); V77I (); K101R ()	10
AD2116	IP	ATV/r,TDF,FTC	V118I (99.9)	L10I (6.5); A71T (1.2); I13V (96.9); V77I (60.0); L63P (100)	10
AD259	IP	IDV/r,AZT,3TC	T69N (5.8)	K103R (6.4); K20R (99.7); M36I (93.35); L33I (100); L63P (100)	5
AD2102	IP	LPV/r,TDF,FTC	L33F (7.5); L33V (6.7)	L10V (3.3); I13V (1.1); K20M (38.5); M36I (89.8); I64V (99.5); L210F (1.9); E138A (100)	5

Table 2: Subjects with mutations associated with an ART-adjusted HIVdb score >0. For the analysis of ART outcomes we only took into consideration mutations detected with 454 sequencing which were associated with an HIVdb score >0 to the ARV regimen started. A treatment-adjusted score was constructed for each patient based on this information. *For example: subject ADZ41 initiated ART with EFV, AZT/3TC. This subject had mutations A98G (2.2%) and E138Q (36.5%). Each mutation has an HIVdb score to EFV of 5. Therefore the treatment-adjusted HIVdb score for this subject was: 5+5=10.*

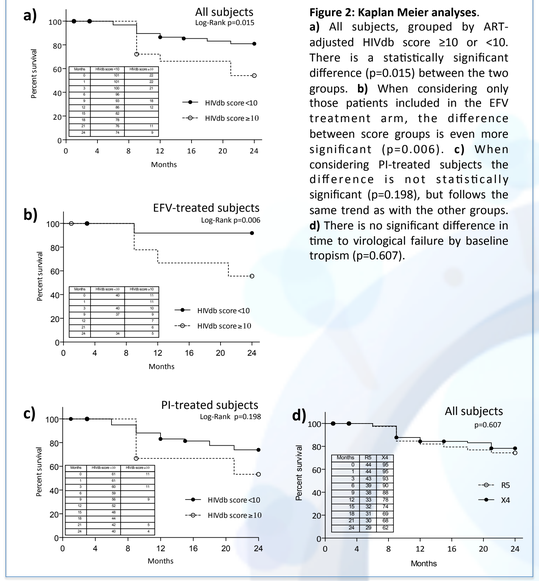


Figure 2: Kaplan Meier analyses. **a)** All subjects, grouped by ART-adjusted HIVdb score ≥10 or <10. There is a statistically significant difference (p=0.015) between the two groups. **b)** When considering only those patients included in the EFV treatment arm, the difference between score groups is even more significant (p=0.006). **c)** When considering PI-treated subjects the difference is not statistically significant (p=0.198), but follows the same trend as with the other groups. **d)** There is no significant difference in time to virological failure by baseline tropism (p=0.607).

		All subjects			EFV- treated			PI- treated		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Gender	Male	1	-	-	1	-	-	1	-	-
	Female	1.650	0.73; 3.70	0.229	2	0.45; 8.93	0.363	2.017	0.74; 5.48	0.169
Age	≥35	1	-	-	1	-	-	1	-	-
	<35	2.07	1.00; 4.34	0.051	0.69	0.08; 5.75	0.734	2.307	0.99; 5.34	0.051
HIVdb score	<10	1	-	-	1	-	-	1	-	-
	≥10	2.62	1.14; 6.25	0.024	5.88	1.31; 26.32	0.021	1.995	0.66; 6.03	0.221
CD4+ T cell counts at baseline (cells/mm3)	≥50	1	-	-	1	-	-	1	-	-
	<50	1.060	0.50; 2.27	0.869	0.57	0.13; 2.55	0.462	1.3	0.51; 3.06	0.624
HIV-1 RNA (copies/ml)	<100.000	1	-	-	1	-	-	1	-	-
	≥100.000	1.070	0.48; 2.38	0.871	1.27	0.25; 6.54	0.775	1.001	0.41; 2.45	0.998
Treatment Group	EFV	1	-	-	-	-	-	-	-	-
	IP	2.185	0.93; 5.11	0.072	-	-	-	-	-	-
Tropism	CCR5	1	-	-	1	-	-	1	-	-
	CXCR4	0.820	0.38; 1.16	0.620	0.55	0.12; 2.46	0.436	0.962	0.39; 2.36	0.934
Risk Group	Heterosexual	1	-	-	1	-	-	1	-	-
	MSM	0.526	023; 1.20	0.127	0.496	0.04; 5.47	0.567	0.489	0.20; 1.18	0.112
	IVDU	0.974	0.32; 2.93	0.963	4.25	0.70; 25.52	0.113	0.335	0.04; 2.55	0.291
	Unknown	1.165	0.15; 8.82	0.883	10.17	0.92; 112.21	0.058	-	-	-
HCV coinfection	No	1	-	-	1	-	-	1	-	-
	Yes	1.201	0.48; 2.96	0.691	4.625	0.93; 22.96	0.061	0.660	0.19; 2.23	0.504
HBV coinfection	No	1	-	-	-	-	-	1	-	-
	Yes	0.722	0.17; 3.03	0.657	-	-	-	0.791	0.18; 3.38	0.752

Table 3: Univariate Cox regression model of risk of virological failure: Baseline factors associated with virological failure were having an HIVdb score ≥10 (p-value=0.024), age <35 years old (p=0.051), and treatment group (p=0.072). When considering only subjects in EFV treatment arm, HIVdb score (p=0.021), and HCV coinfection (p=0.061) were associated with VF. The only factor associated with VF in PI-treated subjects was age (p=0.051). Only factors with univariate P-values <0.1 were included in the multivariate analysis.

		All subjects			EFV-treated			PI-treated		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)	<35	1	-	-	1	-	-	1	-	-
	≥35	0.586	0.26; 1.315	0.195	1.61	0.17; 14.79	0.674	0.52	0.80 ; 1.29	0.16
HIVdb score	<10	1	-	-	1	-	-	1	-	-
	≥10	2.82	1.23; 6.54	0.015	4.56	0.89; 23.41	0.069	1.877	0.62; 5.68	0.26
Treatment Group	EFV	1	-	-	-	-	-	-	-	-
	PI	1.880	0.72; 4.63	0.170	-	-	-	-	-	-
HCV coinfection	(-)	-	-	-	1	-	-	-	-	-
	(+)	-	-	-	3.869	0.76;19.67	0.103	-	-	-

Table 4: Mutivariate Cox regression model of risk of virological failure: Separate models were conbstructed for all subjects, subjects treated with EFV and subjects treated with PIs. The only factor that remained independently associated with an increased risk of virological failure in the multivariate Cox regression model was having a baseline HIVdb score ≥10.

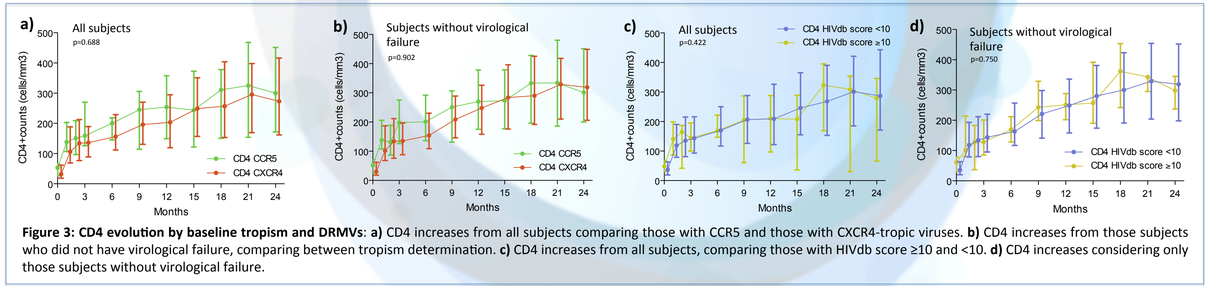


Figure 3: CD4 evolution by baseline tropism and DRMVs: **a)** CD4 increases from all subjects comparing those with CCR5 and those with CXCR4-tropic viruses. **b)** CD4 increases from those subjects who did not have virological failure, comparing between tropism determination. **c)** CD4 increases from all subjects, comparing those with HIVdb score ≥10 and <10. **d)** CD4 increases considering only those subjects without virological failure.

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