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insight

SMART STUDY

NNRTI Clearance Rates, Drug-resistance Profiles and Virologic Outcomes of Patients Stopping and Restarting NNRTI-based cART in SMART

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INTRODUCTION

- Interrupting HAART is generally discouraged.
- There are circumstances when interruption may be required or may occur unplanned due to patient choice or problems with drug supply.
- Due to the long half-life of NNRTIs (>20 h), interrupting NNRTI-based HAART may result in a period of inadvertent monotherapy with the associated risk of resistance.

AIMS OF THE STUDY

- Characterise patients interrupting NNRTI-based HAART within SMART.
- Determine the relationship between modality of interruption, sensitive assessment of NNRTI clearance rates and drug resistance after interruption, and responses to restarting NNRTI-based HAART.

METHODS

Week 4 post-interruption:

- EFV (n=39) and NVP (n=31) plasma concentrations determined by sensitive HPLC
  - Lower limit of quantification 5 ng/ml for EFV and 0.5 ng/ml for NVP
- Pharmacogenomic predictors of EFV clearance: Cytochrome P450 2B6 (*CYP2B6*) 516G>T (n=110) and nuclear Constitutive androstane receptor (*CAR*) (rs2307424) (n=114) SNPs genotyped by real-time PCR.

Week 4-10 post-interruption:

- Resistance testing by population sequencing (PS, n=112), AS-PCR targeting the NRTI RAMs M41L, K65R, M184V, T215Y and T215F and the NNRTI RAMs K103N, Y181C, Y188L, and G190A (n=124, pre-defined interpretative cut-offs), UDS spanning RT regions aa 100-138 and 179-190 (n=21, interpretative cut-off 1%)

Study population

		Overall n=132	Interruption modality			P
			Simultaneous n=63	Staggered n=46	Switched n=23	
Gender, n (%)	Male	99 (75.0)	47 (74.6)	32 (69.6)	20 (87.0)	*0.29*
Risk group, n (%)	Homosexual	61 (46.2)	31 (49.2)	18 (39.1)	12 (57.2)	*0.06*
	Heterosexual	41 (31.1)	20 (31.8)	18 (39.1)	3 (13.0)	
	Other/Unknown	30 (22.7)	12 (19.0)	10 (21.7)	8 (34.8)	
Ethnicity, n (%)	Black	51 (38.6)	22 (34.9)	21 (45.7)	8 (34.8)	*0.60*
	White	63 (47.7)	34 (54.0)	18 (39.1)	11 (47.8)	
	Other/unknown	18 (13.6)	7 (11.1)	7 (15.2)	4 (17.4)	
Age, median yrs (IQR)		45 (39, 52)	44 (39, 50)	48 (41, 52)	45 (41, 54)	*0.28*
CD4, median cells/mm^3 (IQR)		645 (475, 793)	624 (475, 833)	657(461, 758)	643 (527, 751)	*0.88*
Nadir CD4, median cells/mm^3 (IQR)		207 (90, 308)	212 (115, 374)	199 (67, 303)	205 (70, 300)	*0.44*
VL recorded as <50 cps/ml, n (%)		67 (50.8)	26 (41.3)	29 (63.0)	12 (52.2)	*0.08*
ART exposure, median years (IQR)		6 (3, 9)	6 (3, 9)	7 (3, 9)	6 (3, 10)	*0.77*

80/132 (60.6%) patients on EFV, 51/132 (38.6%) on NVP and 1/132 (0.8%) on DLV.

Pharmacokinetics

- At week 4 post-interruption 35/39 (89.7%) and 19/31 (61.3%) patients had detectable EFV or NVP, respectively
- Median (IQR) concentrations 16 (9, 55) and 0.96 (0.5, 3.2) ng/ml for EFV and NVP, respectively.

Pharmacogenomics

***CYP2B6* 516 G>T:**

- GG 73/110 (66.4%)
- GT 31/110 (28.2%)
- TT 6/110 (5.4%)

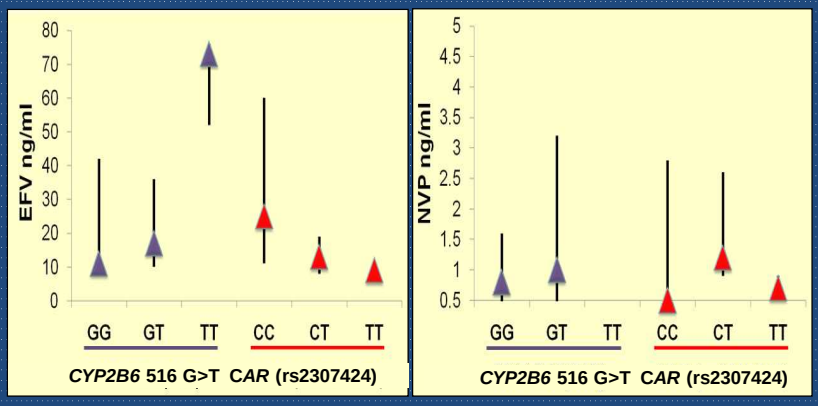
(EFV *vs.* NVP p=0.84)

***CAR* (rs2307424):**

- CC 76/114 (66.7%)
- CT 29/114 (25.4%)
- TT 9/114 (7.9%)

(EFV *vs.* NVP p=0.20)

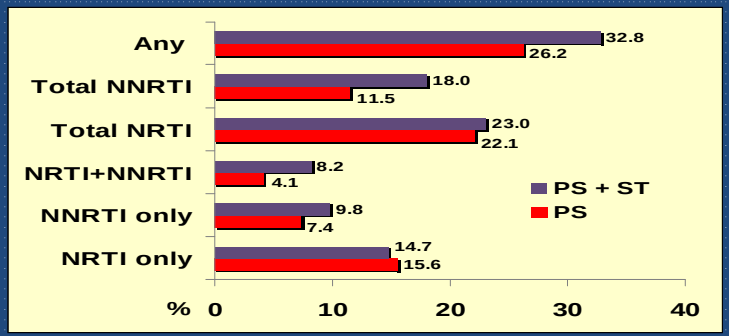
Median (IQR) EFV and NVP plasma concentrations at week 4 after interruption according to *CYP2B6* 516G>T and *CAR* (rs2307424) genotypes



For **EFV**: *CYP2B6* 516 GG *vs.* TT p=0.02, GG/GT *vs.* TT p=0.01; *CAR* (rs2307424) CC *vs.* CT p=0.08, CC *vs.* TT p=0.32, CC *vs.* CT/TT p=0.051.

Prevalence of RAMs by population sequencing (PS) and sensitive testing (ST) at wk 4-10 after interruption

≥1 RAM: 32/122 (26.2%) patients by PS
40/122 (32.8%) by combined PS + ST



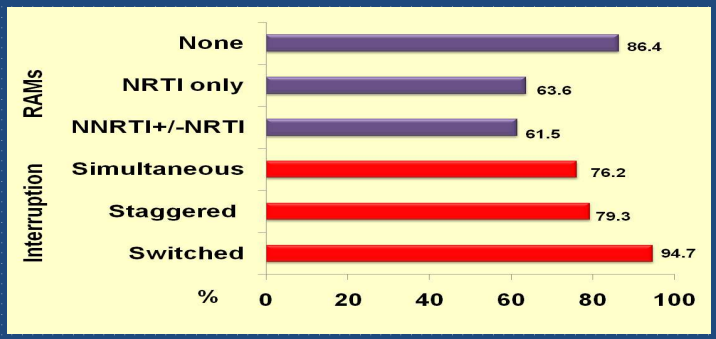
Relative to AS-PCR, UDS detected 1 additional G190A (frequency 4%) in a sample also containing K103N and Y181C, and 2 additional M184V (3% and 19% respectively).

Predictors of drug resistance in multivariable analyses

- **Detection of NRTI RAMs was associated with:**
  - **CD4 nadir**
    (OR 0.68 for each 50 cells/mm³ higher; 95% CI 0.52, 0.87; p=0.003)
  - **duration of ART exposure prior to interruption**
    (OR 1.26 for each year longer; 95% CI 1.10, 1.45; p=0.001)
  - **modality of interruption**
    (OR 4.25 for staggered vs simultaneous interruption; 95% CI 1.02, 17.77;p=0.03)
- **Detection of NNRTI RAMs was associated with:**
  - **VL recorded as <50 cps/ml at the time of interruption**
    (OR 0.28; 95% CI 0.09, 0.91; p=0.03).
- **Prevalence of NNRTI RAMs** was 2/34 (5.9%) among patients with concentrations <15 ng/ml for EFV and <1.0 ng/ml for NVP *vs.* 10/31 (32.3%) in patients with higher concentrations (p=0.007).

Virologic responses to restarting HAART

- The analysis of responses to restarting therapy was restricted to 90 patients who restarted NNRTI-based HAART without a PI.
- Between 4 and 12 months after restarting , 73/90 (81.1%) patients regained VL suppression <400 cps/ml.



Predictors of regaining a VL<400 cps/ml 4-12 months after restarting cART

		Univariable results			Multivariable results		
		OR	95% CI	*P*	OR	95% CI	*P*
Gender	Male	1.00	-	*0.38*	1.00	-	*0.22*
	Female	0.60	0.19, 1.85		0.41	0.10, 1.68	
Age	Each 5 yrs older	1.04	0.78, 1.39	*0.79*	1.09	0.71, 1.68	*0.70*
Time on ART pre-interruption	Each yr longer	0.91	0.80, 1.03	*0.15*	0.89	0.75, 1.07	*0.21*
CD4 at interruption	Each 50 cells higher	1.05	0.91, 1.19	*0.52*	1.06	0.89, 1.27	*0.50*
VL recorded as <50 cps/ml at interruption	No	1.00	-	*0.87*	1.00	-	*0.99*
	Yes	1.09	0.38, 3.15		1.00	0.27, 3.72	
Time to restarting cART	Each wk longer	1.01	0.99, 1.04	*0.21*	1.02	0.99, 1.06	*0.11*
NNRTI restarted	EFV	1.00	-	*0.28*	1.00	-	*0.38*
	NVP	0.55	0.19, 1.61		0.55	0.15, 2.09	
Interruption modality	Simultaneous	1.00	-	*0.27*	1.00	-	*0.20*
	Staggered/Switched	1.83	0.63, 5.34		2.62	0.60, 11.38	
RAMs	None	1.00	-	*0.03*	1.00	-	*0.04*
	NRTI only	0.24	0.06, 1.01		0.17	0.03, 1.15	
	NNRTI +/- NRTI	0.22	0.06, 0.84		0.18	0.03, 0.89	

In logistic regression analyses, regaining a VL<400 cps/ml was affected by the detection of RAMs during interruption.
The effect was similar when considering RAMs detected by PS or ST alone.

CONCLUSIONS

- 81% of patients with suppressed viremia who interrupted and restarted NNRTI-based HAART regained virologic suppression.
- High prevalence of NRTI and NNRTI RAMs in the rebound viremia.
- A switched interruption modality should be preferred over a staggered interruption in NRTI-experienced patients to reduce the reselection of archived NRTI mutations.
- Sensitive testing allowed an improved appreciation of the full extent of NNRTI resistance with good overall agreement between AS-PCR and UDS.
- Simultaneous interruption of suppressive NNRTI-based HAART carries an 18% risk of NNRTI resistance, which correlates with slow NNRTI clearance.

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