Detection of NNRTI resistance mutations after interrupting NNRTI-based regimens

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on behalf of UK HIV Drug Resistance Database & UK CHIC study.

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BACKGROUND

There is evidence that NNRTI mutants emerge after interruption of suppressive NNRTI-based ART, due to the long half-life of NNRTIs. This has implications for both loss of treatment options for people undergoing ART interruption and potential transmission of drug resistance.

The aim of this study was to quantify the extent to which NNRTI mutations can be detected in the rebound viremia following interruption of suppressive NNRTI-based ART.

METHODS

The study population comprised patients from the UK HIV Drug Resistance Database and from the UK Collaborative HIV Cohort study (UK CHIC).

Figure 1 illustrates the eligibility criteria and the size of the population eligible for the analysis.

Virologic failure is defined as a VL>200 copies/ml, after at least 6 months on a certain regimen.

Resistance

Only resistance tests conducted after treatment interruption (TI) while off ART were considered.

NNRTI resistance was defined as at least one major NNRTI mutation according to the IAS-USA list (2008).

Statistical analysis

- Firstly, it was assessed whether there were significant differences, for the covariates listed below, between those who had a resistance test performed during the TI and those who did not. Chi-square test for categorical variable and Kruskal Wallis test for continuous variables were used. Crude and adjusted relative risks (RR) of having a resistance test performed after TI were calculated using a modified Poisson regression approach.

- Covariates considered include: demographic variables, calendar year of TI, whether the viral load (VL) was below 50 copies/ml at TI, length of virologic suppression, whether a resistance test was conducted pre-ART, time from ART initiation to TI, CD4 count at TI and CD4 count nadir, type of antiretroviral drug at TI and type and number of antiretroviral drugs experienced before TI (not shown).

- For the main analysis, the same approach was used to identify predictors of having NNRTI resistance detected in the rebound viremia after TI.

- Additional covariates considered include time from TI to resistance test, CD4 count at resistance test off-ART and subtype
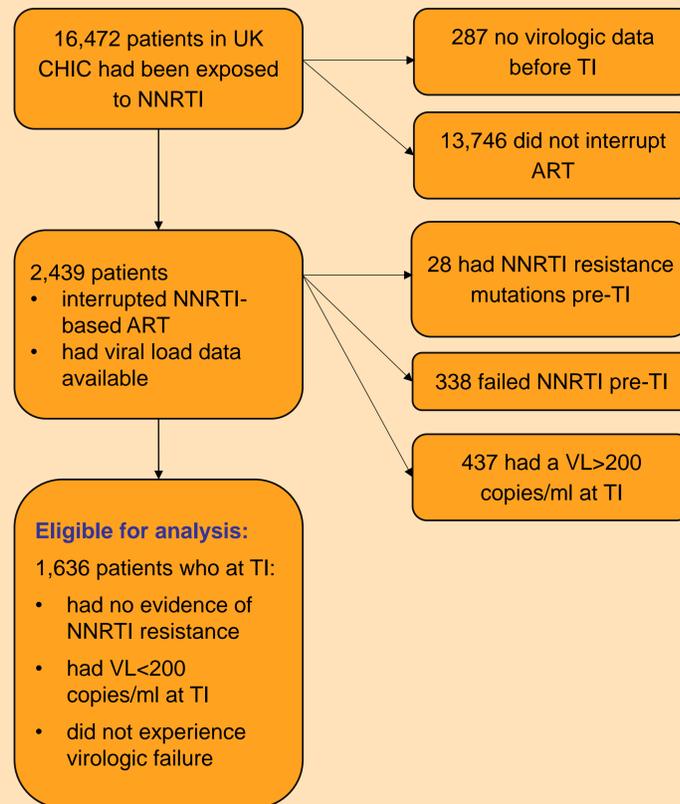
RESULTS

Figure 1. Overview of patients eligible for the analysis

16,472 patients in UK CHIC had been exposed to NNRTI

→ 287 no virologic data before TI

→ 13,746 did not interrupt ART

2,439 patients
- interrupted NNRTI-based ART
- had viral load data available

→ 28 had NNRTI resistance mutations pre-TI

→ 338 failed NNRTI pre-TI

→ 437 had a VL>200 copies/ml at TI

Eligible for analysis:

1,636 patients who at TI:
- had no evidence of NNRTI resistance
- had VL<200 copies/ml at TI
- did not experience virologic failure

Predictors of resistance test availability

- Of 1,636 eligible patients, 13% (n=208) had a resistance test performed after stopping suppressive NNRTI-based ART. Table 1 illustrates the characteristics of the people who did and did not have a resistance test after treatment interruption.

- The covariates significantly associated with the presence of a resistance test after TI (mode of infection, age, calendar year of TI, maximum VL achieved, length of time with VL<200 copies/ml, years from ART initiation to TI, most recent CD4 count at TI, CD4 nadir, being on NVP, EFV, AZT, 3TC, TDF, FTC) were considered in a multivariate model.

- Independent predictors of having a resistance test were:

  - older calendar year of TI (range 1997-2008, aRR per 1 more recent calendar year = 0.89; 95% confidence interval [CI]: 0.85-0.93; p<0.0001)

  - higher maximum VL on ART pre-TI (aRR per 1 log increase=1.14; 95% CI: 1.04-1.26; p=0.0042)

  - younger age (aRR per 1 year older = 0.96; 95%CI: 0.94-0.97; p<0.0001)

  - higher CD4 count nadir (aRR per 100 cells/µl increase=1.08; 95%CI: 1.04-1.12; p<0.0001)

  - being on 3TC at ART interruption (aRR = 1.99; 95%CI: 1.39-2.87; p<0.0001).

Detection of NNRTI resistance mutations

- Among the 208 individuals with a resistance test performed after stopping suppressive NNRTI-based ART (see characteristics in table 1), **12% (n=25, 95% CI: 8%-17%) had ≥1 NNRTI resistance mutation detected at the first resistance test following ART treatment interruption.**

- **In those with at least 1 NNRTI resistance mutation detected the median time between TI and the resistance test was 12 months (IQR: 3-20 months).**

- The distribution of NNRTI resistance mutations, when detected after ART interruption is illustrated in Figure 2. K103N was the most prevalent mutation. There was no occurrence of K101H/P, V106M, Y181/V, Y188C/H or G190S.
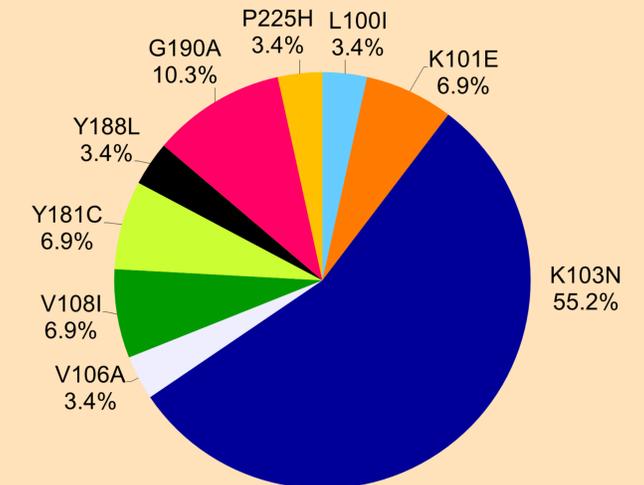
Table 1. Baseline characteristics

		All eligible patients (n=1,636)		Patients with a resistance test after TI (while off-ART)		
				Yes (n=208)	No (n=1,428)	p
Male, n (%)		1,137	(69%)	136 (65%)	1,001 (70%)	0.1678
Ethnicity*, n (%)	White	885	(54%)	113 (56%)	772 (55%)	0.4005
	Black	595	(36%)	71 (35%)	524 (38%)	
	Other	115	(7%)	19 (9%)	96 (7%)	
Mode of infection**, n (%)	MSM	732	(45%)	115 (57%)	617 (47%)	0.0089
	HT	683	(42%)	80 (40%)	603 (46%)	
	Other	97	(6%)	6 (3%)	91 (7%)	
Age, med (IQR)		38	(33-45)	35 (30-40)	38 (33-45)	<.0001
Calendar year of TI, med (IQR)		Apr04	(Feb02; Dec06)	Jan03 (Sep01; Sep04)	Sep04 (Mar02; Apr07)	<.0001
VL at TI <50 copies/ml, n (%)		1,421	(87%)	172 (83%)	1,249 (87%)	0.0600
Maximum VL on ART, med (IQR)		251	(50-2,703)	406 (60-20,536)	230 (50-1,974)	0.0033
Months with VL<200 copies/ml, med (IQR)		12	(4-30)	6 (2-21)	12 (4-32)	<.0001
Resistance test pre-ART, n (%) (if done, no NNRTI mutations were detected)		384	(23%)	51 (25%)	333 (23%)	0.7029
Years ART initiation - TI, med (IQR)		1.70	(0.63-3.62)	1.05 (0.40-2.71)	1.77 (0.68-3.69)	<.0001
Most recent CD4 count (cells/µl) at TI, med (IQR)		415	(271-586)	456 (305-640)	408 (270-576)	0.0102
CD4+ nadir count (cells/µl), med (IQR)		295	(140-466)	379 (230-513)	280 (135-453)	<.0001
NNRTI at TI, n (%)	NVP	779	(48%)	127 (61%)	652 (46%)	<.0001
	EFV	864	(53%)	81 (39%)	783 (55%)	<.0001
	Other	5	(0%)	1 (0%)	4 (0%)	0.6243
NRTI at TI, n (%)	AZT	778	(48%)	132 (48%)	646 (45%)	<.0001
	DdC	2	(0%)	1 (0%)	1 (0%)	0.2382
	DdI	176	(11%)	20 (7%)	156 (11%)	0.5692
	D4t	229	(14%)	33 (12%)	196 (14%)	0.4060
	3TC	1,179	(72%)	177 (64%)	1,002 (70%)	<.0001
	ABC	253	(15%)	34 (12%)	219 (15%)	0.7066
	TDF	369	(23%)	21 (8%)	348 (24%)	<.0001
	FTC	240	(15%)	8 (3%)	232 (16%)	<.0001

MSM: men having sex with men; HT: heterosexual; med: median; IQR: interquartile range; *n=2440; **n=2351; ***n=2181

Detection of NNRTI resistance mutations

Figure 2. NNRTI resistance mutations detected after NNRTI interruption

Pie chart segments: K103N 55.2%, K101E 6.9%, L100I 3.4%, P225H 3.4%, G190A 10.3%, Y188L 3.4%, Y181C 6.9%, V108I 6.9%, V106A 3.4%

- The only independent predictor of NNRTI resistance being detected (in a multivariate model including CD4 cell count at TI, CD4 nadir and NVP at TI) was CD4 nadir (aRR for 100 cells/µl increase in CD4 nadir = 0.67; 95% CI: 0.53-0.85; p=0.001).

Sensitivity analysis

1. Patients who stopped their ART regimen while having a VL ≤ 50 copies/ml (n=1,421, 87%) with a resistance test after TI (172/1421, 12%)
   - 12% (20; 95%CI: 7-17%) had NNRTI resistance

2. People who had a resistance test performed within 2 months since TI (n=55/208, 26%).
   - 7% (4; 95% CI: 3-19%) had NNRTI resistance

3. People who had a resistance test performed within 6 months since TI (n=94/208, 45%).
   - 9% (8; 95% CI: 4-17%) had NNRTI resistance

4. Simultaneous TI, with resistance test (n=188):
   - 12% (23; 95% CI: 7-17%) had NNRTI resistance

5. Staggered TI, with resistance test (n=20):
   - 10% (2; 95% CI: 1-32%) had NNRTI resistance

CONCLUSIONS

- To our knowledge this is the largest study to evaluate the detection of NNRTI resistance in the rebound viremia that follows interruption of a suppressive NNRTI-based regimen.

- It confirms that resistance is a relatively common phenomenon, occurring in 12% of patients tested.

- These estimates support the concept that interruption of EFV or NVP based ART carries a significant risk to the patient and informs models that incorporate HIV drug resistance emergence and transmission.