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Comparison of the rate of emergence of drug resistant HIV variants at virological failure in HAART combinations containing tenofovir, efavirenz and lamivudine or emtricitabine within UK CHIC

Naomi Bulteel, Mark Nelson, Caroline Sabin, David Dunn
On behalf of UK CHIC and the UK HDRD

UK HIV
Drug Resistance Database

CHIC

Background

- Lamivudine (3TC) and emtricitabine (FTC) are guideline choices for combination highly active antiretroviral therapy (HAART)

- Despite similar chemical structures, different pharmacokinetic and pharmacodynamic properties are reported between the two agents

- Studies have suggested that the emergence of resistance mutations is more frequent with 3TC containing regimens.

Methods

- Inclusion criteria
  - All patients receiving tenofovir (TDF) and efavirenz (EFV) with either 3TC or FTC within UK CHIC

- Exclusion criteria:
  - Individuals receiving more than 3 antiretroviral agents
  - Individuals with a resistance test revealing either K65R or M184V mutation

- Endpoints
  - Detection of M184V
  - Detection of K65R
  - Detection of either M184V or K65R

Statistics

- Rate of event = number of events divided by person time

- Rates were stratified by demographic variables (age, sex, risk factor and ethnicity), current CD4 count and current viral load

- Significant associations determined by Poisson regression

- Virological failure = 1 viral load > 400 copies/ml

- For sensitivity analyses, only the first regimen was analysed and logistic regression was used to determine significant associations between type of regimen and detection of resistance mutations

Baseline characteristics

		3TC + TDF + EFV	FTC + TDF + EFV
Total number		1228	5190
Age	Median (IQR)	39 (34, 45)	40 (34, 46)
Sex n (%)	Male	981 (79.9)	4268 (82.2)
	Female	247 (20.1)	922 (17.8)
Ethnicity n (%)	White	767 (62.5)	3111 (59.9)
	Black	341 (27.8)	1438 (27.7)
	Other	120 (9.8)	641 (12.4)
Risk factor n (%)	MSM	713 (58.1)	3053 (58.8)
	Heterosexual	392 (31.9)	1480 (28.5)
	IVDU	46 (3.8)	109 (2.1)
	Other/unknown	77 (6.3)	548 (10.6)
CD4 (cells/mm^3)	Median (IQR)	276 (170, 470)	297 (192, 475)
VL (copies/ml)	Median (IQR)	53 (50, 82000)	312 (50, 66249)
VL ≤ 50 n (%)[1]	Yes	514 (49.9)	1992 (46.1)
	No	517 (50.1)	2326 (53.9)

[1]Amongst those receiving 3TC, 197 did not have a VL measured at start of regimen. Amongst those receiving FTC, 872 did not have a VL measured at start of regimen.

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Results

- 5455 patients received either (or both) 3TC, TDF and EFV or FTC, TDF and EFV through the course of follow up contributing a total of 6465 cases

- 47 episodes preceded by a resistance test showing evidence of K65R (n=4) or M184V (n=43) therefore excluded

- 9962 person-years follow up

Results

- Detection of M184V
  - 38 cases of M184V detected (event rate 0.38(95% CI: 0.26,0.5)/100 person years)

  - M184V development more common with 3TC than FTC (0.55 (0.28,0.96)/100 person years vs. 0.34 (0.21,0.46)/100 person years)

  - Patients of black ethnicity more likely to develop M184V

		M184V	
		RR (95% CI)	P-value
Regimen	FTC 3TC	1 1.55 (0.78, 3.08)	0.23
Current CD4 (cells/mm3)	≤200 201 – 350 >350 Missing	1.49 (0.74, 2.97) 0.83 (0.4, 1.73) 1 1.42 (0.27, 7.35)	0.17
Current age (years)	≤35 36 – 45 >45	1.45 (0.93, 2.26) 0.83 (0.53, 1.32) 1	0.24
Ethnicity	White Black Other	1 2.86 (1.44, 4.68) 0.64 (0.14, 2.82)	0.003

Results

- Detection of K65R
  - 21 cases of K65R detected over 9962 person years (event rate 0.21 (95% CI:0.12,0.31)/100 person years)

  - K65R development more common with 3TC than FTC (0.32 (0.13,0.66)/100 person years) v 0.18 (0.1,0.3)/100 person years)

  - Higher current CD4 counts less likely to be followed by the detection of K65R (0.77 (0.65, 0.91) per 50 cells higher)

		K65R	
		RR (95% CI)	P-value
Regimen	FTC 3TC	1 1.62 (0.65, 4.02)	0.3
Current CD4 (cells/mm3)	≤200 201 – 350 >350 Missing	0.77 (0.65, 0.91)	0.003
Current age (years)	≤35 36 – 45 >45	Excluded[1]	
Ethnicity	White Black Other	1 1.88 (0.77, 4.6) -	0.16

[1]Adjusted for ethnicity – no other factors significant in univariable analyses

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Results

- Detection of K65R or M184V
  - 48 cases of either K65R or M184V (event rate 0.48(95% CI: 0.26,0.5)/100 person years)

  - No association seen between type of regimen and detection of K65R or M184V (1.43 (0.77,2.66); p = 0.27)

  - Black ethnicity and low current CD4 count were more likely to be associated with detection of M184V or K65R

		K65R or M184V	
		RR (95% CI)	P-value
Regimen	FTC 3TC	1 1.43 (0.77, 2.66)	0.27
Current CD4 (cells/mm3)	≤200 201 – 350 >350 Missing	1.73 (0.91, 3.26) 0.77 (0.39, 1.51) 1 1.4 (0.3, 6.62)	0.02
Current age (years)	≤35 36 – 45 >45	1.4 (0.94, 2.1) 0.95 (0.64, 1.42) 1	0.26
Ethnicity	White Black Other	1 3.32 (1.46, 7.53) 0.53 (0.12, 2.31)	0.003

Results

- Patients experiencing virological failure with resistance tests available at time of failure
  - 53 patients were receiving 3TC based regimens
  - 148 patients were receiving FTC based regimens
  - Of those receiving 3TC, 7 (13.2%), 12 (22.6%) and 15 (28.3%) of patients developed K65R, M184V and either K65R or M184V respectively
  - Of those receiving FTC, 13 (8.8%), 20 (13.5%) and 26 (17.6%) developed the above mutations

Sensitivity analyses

		K65R		M184V		K65R/M184V	
		OR(95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Univariable analyses							
Regimen	FTC	1	0.36	1	0.12	1	0.09
	3TC	1.58 (0.59, 4.20)		1.87 (0.84, 4.16)		1.85 (0.89, 3.85)	
Multivariable analyses[1]							
Regimen	FTC	1	0.63	1	0.12	1	0.1
	3TC	1.57 (0.58, 4.24)		1.91 (0.85, 4.32)		1.89 (0.89, 4.01)	

[1]Adjusted for ethnicity – no other factors significant in univariable analyses

Conclusions

- Virological failure of TDF, EFV and 3TC or FTC is uncommon in clinical practice
- Although 3TC containing regimens were associated with an increased rate of M184V and K65R detection this failed to reach statistical significance
- Other factors, particularly cost, may become increasingly important in choosing between these agents where such high rates of virological success are achieved

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Questions?