No Effect of HIV-1 Subtype C on Virological Failure Rate with First-line TDF Regimens

Ellen White[1], Erasmus Smit[2], Duncan Churchill[3], Simon Collins[4], Clare Booth[5], Anna Tostevin[1], Caroline Sabin[6], Deenan Pillay[7,8], David T Dunn[1], on behalf of UKHDRD and UKCHIC.

[1]MRC Clinical Trial Unit at UCL, London, United Kingdom, [2] Public Health England, Birmingham Heartlands Hospital, Birmingham, United Kingdom, [3]Brighton and Sussex Hospitals NHS Trust, Brighton, United Kingdom, [4]HIV i-Base, London, United Kingdom, [5]Royal Free London NHS Foundation Trust, London, United Kingdom, [6]Department of Infection and Population Health, UCL, London, United Kingdom , [7]Division of Infection and Immunity, UCL, London, United Kingdom, [8]Africa Centre for Population Health, University of KwaZulu-Natal, South Africa

Contact information:
Miss Ellen White
Email:
ellen.white@ucl.ac.uk
http://www.hivrdb.org.uk

UKHIV Drug Resistance Database

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Background

- HIV-1 subtype C viruses have a predisposition to develop K65R [1,2].
- This appears to be due to **different codon usage**:

Subtype B	**AAG**	**AAA**	**AAA**
Subtype C	**AAA**	**AAG**	**AAG**
Codon	**64**	**65**	**66**

- **Subtype C** is **the most common** viral subtype worldwide (≈50%) [3].
- This is a concern since **tenofovir**, which **selects for K65R**, is expanding in use since WHO recommendation in 2013.
- A recent **multinational study** indicated that patients with **subtype C** were at an **increased risk** of virological failure [4].
- We have **compared virological failure rates by subtype** using the results of routine genotypic tests reported to the UK HIV Drug Resistance Database, with a larger number of subtype C viruses.

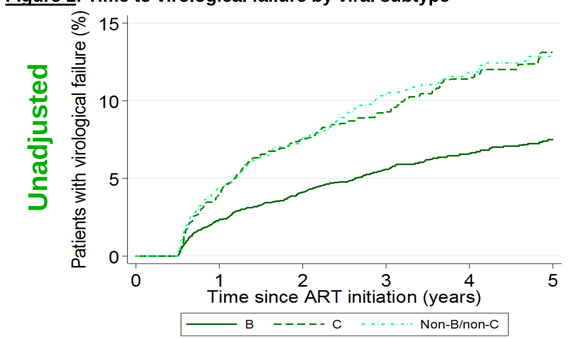
References

1. Brenner, AIDS 2006, 20:F9-13
2. Smit et al, CROI 2015 [Abstract No. 596]
3. Hemelaar et al, AIDS 2006, 20: W13-23
4. Kantor et al , CID 2015, 60: 1541-9

Analysis

- **Subtype B** patients were mostly **white** (83%) and **MSM** (85%)
- **Subtype C** mostly **black** (70%) and **heterosexual** (79%)
- **Subtype non-B/C** patients were demographically more **mixed** (35% white, 53% black; 26% MSM, 63% heterosexual).
- **8746 patients** were included and followed up for a median of **3.3 years**
- **5465** (4123 observed, 1342 average of imputed) were **subtype B**, **1455** (823, 632) **subtype C**, and **1826** (1203, 623) **non-B/C**

Figure 1: Time to virological failure by viral subtype



- Risk of virological failure for **subtype non-B/C** (**12.8%** at 5 years) was similar to **subtype C** (**13.1%**). **Subtype B** had a lower risk of VF (**7.5%**).

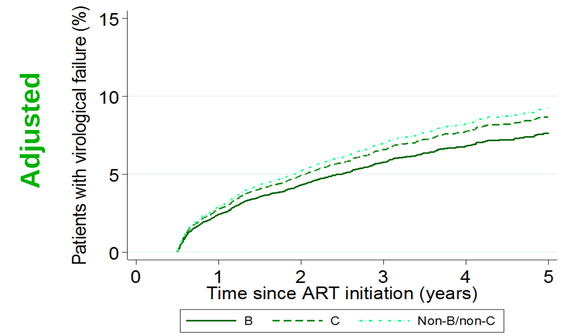
Table 1: Predictors of virological failure

	Total	HR	aHR*	95% CI	p-value
Subtype					
B	5465	0.54	0.87	0.63-1.21	0.41**
C	1455	1.00	1.00	---	
Non-B Non-C	1826	1.00	1.06	0.81-1.40	0.65**
Exposure group					<0.001
MSM	5127	1.00	1.00	---	
MSF	1342	2.26	1.63	1.21-2.21	
FSM	1623	2.14	1.47	1.07-2.00	
Ethnicity					0.04
White	5367	1.00	1.00	---	
Black	2499	1.91	1.33	1.03-1.71	
Asian	321	0.89	0.79	0.48-1.32	

*Adjusted for other variables in table, ART regimen, baseline CD4, baseline viral load, year of ART initiation
**P-values from individual Wald tests
Values shown are averages over imputed datasets

The **subtype** difference disappeared in adjusted analyses (**aHR=0.9, 95% CI 0.6-1.2, P=0.41**), mediated by the effects of exposure group and ethnicity.

Figure 2: Time to virological failure by viral subtype from adjusted Cox model



- **Exposure** group was the strongest predictor of VF, lower rates among MSM.
- **Ethnicity** was also a predictor of virological failure, lower rates were among White and Asian patients.

Methods

- Included patients enrolled in the UK CHIC study initiating a **TDF-containing first line** regimen with XTC and EFV or NVP or LPV/r or DRV/r or ATV/r
- **Virological failure**: 2 consecutive viral loads **>200 copies/mL** after 6 months on treatment
- Most had subtype determined from pre-ART resistance test (but not a prerequisite)
- **Multiple imputation** was used to fill in the missing **subtypes** based on demographic and clinical data

Conclusions

- Strong clinical data to show that subtype differences in K65R are not observed in treatment outcome
- Strengths – Large sample in a single health system
- Treatment outcome is related to demographic factors (exposure & ethnicity) rather than subtype
- Reassuring finding for expanded use of TDF in areas where subtype C virus predominates (southern Africa and India)
- Tenofovir regimens are a durable first-line regimen regardless of subtype, with an average of 9.4% failing first line at 5 years

Acknowledgements

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