K65R detected more frequently in HIV-1 subtype C viruses at virological failure

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Background

- Cell culture experiments have shown that subtype C viruses have a greater propensity to develop the K65R mutation [1].
- This appears to be due to different codon usage:

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

- The clinical relevance of this finding has not been elucidated. A high prevalence of K65R has been documented in several cohort studies in Southern Africa, where subtype C is the predominant subtype [2,3]. However, prolonged virological failure could also account for this observation.
- A retrospective European study found that K65R selection was significantly higher in subtype C but included a limited number of subtype C viruses [4].
- We have performed a similar analysis using the results of routine genotypic tests reported to the UK HIV Drug Resistance Database, with a much larger number of subtype C viruses and a range of different regimens.

Analysis

K65R prevalence over time

- The prevalence of K65R by year of sampling was compared for subtype B and C viruses among patients with virological failure.
- Subtype C viruses consistently showed a higher prevalence of K65R.
- The peak frequency of K65R appeared to be earlier for subtype B (2003, 10%) than for subtype C (2007, 14%).

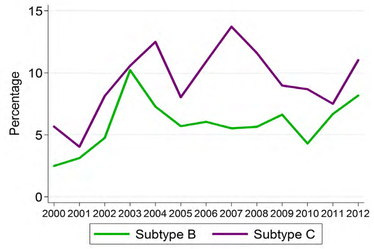
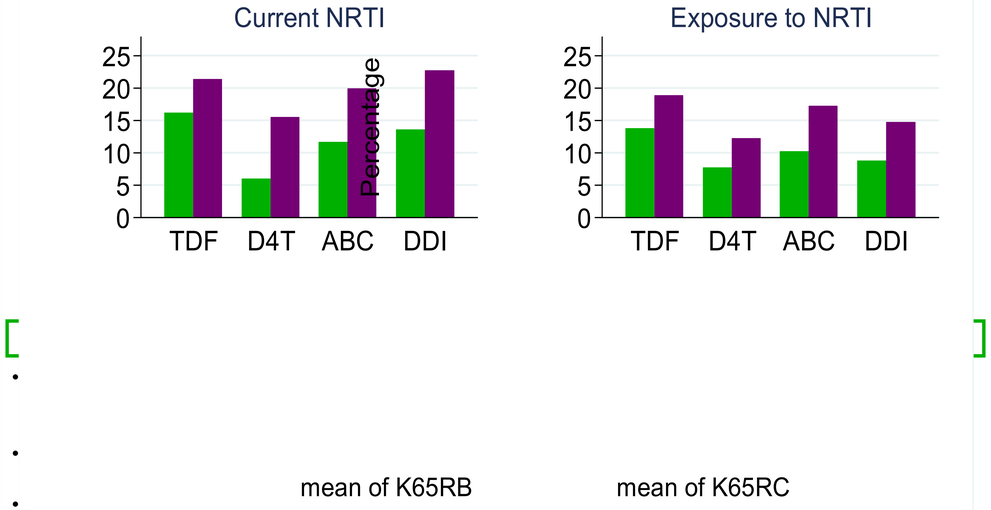


Figure 1: Percentage of K65R mutation in ART-experienced patients by subtype, 2000-2012 (with ≥1 IAS mutation)

Cumulative K65R resistance by NRTI exposure

- Further analyses focussed on patients with a complete ART history (via linkage with UK CHIC study).
- Tests with no IAS mutations were excluded.
- For patients with multiple tests we considered the first test when K65R was detected, or the last test if never detected.
- Each test was classified by current and ever exposure to ABC, TDF, d4T, ddI (drugs which primarily select for K65R).
- 4,242 patients were included in the analysis (3,439 Subtype B, 803 Subtype C)
- K65R was observed in 7.8% of subtype B viruses and 14.5% of subtype C viruses.



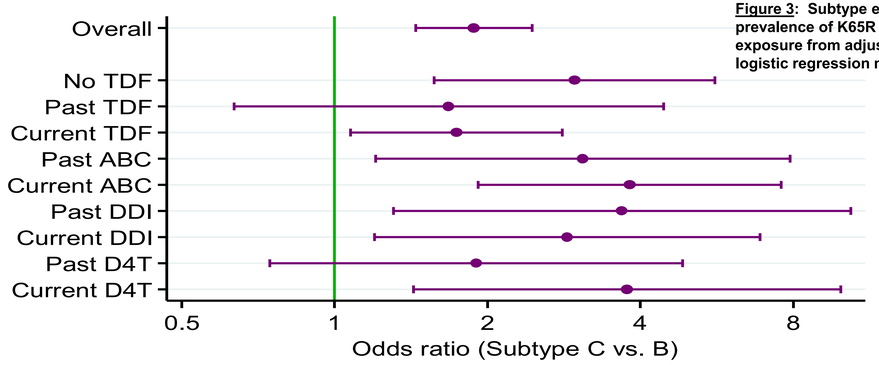


Figure 3: Subtype effect on prevalence of K65R by drug exposure from adjusted logistic regression model

Summary

- These are the strongest clinical data yet to show an increased risk of selection of the K65R mutation among subtype C viruses.
- This effect was observed across a range of different NRTI exposure histories.
- Preliminary analysis (not shown) suggest that non-B non-C subtypes have a similar prevalence of K65R to subtype B.
- A key unresolved clinical question is whether patients infected with subtype C viruses are at a higher intrinsic risk of virological failure on first-line TDF-containing regimens. We are currently undertaking such analyses.

References

1. Brenner et al; AIDS 2006, 20:F9-F13
2. Sunpath et al; AIDS 2012, 26(13) 1679-1684
3. Skhosana et al; PLoS ONE, 2015, 10(2): e0118145
4. Theys et al; Antimicrob Agents Chemother , 2013, 57(2): 1053-1056

Acknowledgments

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