UCL

Source of HIV-1 drug-resistant minority variants in people who are recently infected

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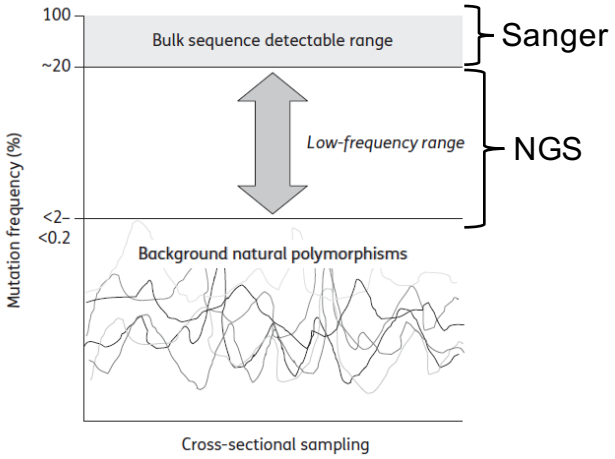
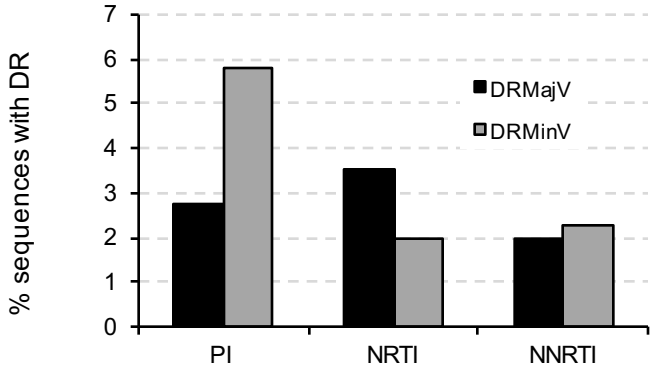
Introduction

- Genotypic antiretroviral resistance testing plays an important role in clinical management of people infected with HIV
- Currently, Sanger population-based sequencing is used
- Sanger technology being replaced by next generation sequencing (NGS) in NHS microbiology laboratories
- The clinical significance of drug-resistant minority variants (DRMinV) present at <20% variant frequency remains to be fully determined

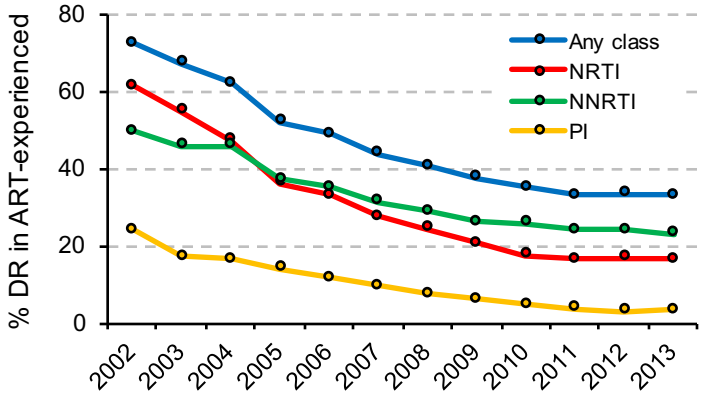


(Baxter *et al*., 2000; Cohen *et al*., 2002; Durant *et al*., 1999; Melnick *et al*., 2000; Meynard *et al*., 2000; Tural *et al*., 2002; Johnson & Geretti, 2010)

Enhanced surveillance of HIV-1 DR



Recent MSM (NGS)



All exposure groups (UK HDRD)

- >50% new HIV-1 diagnoses tested for incidence using RITA
- Identified recent MSM samples were tested by NGS between 2011 and 2014 (*n=655*)
- Prevalence of DR doubles when DRMinV are included from 8.1% to 17.4%
- Majority (62%) of DRMinV were against PIs
- In contrast, the frequency of DR majority variants (DRMajV) in ART-experienced is lowest against PIs

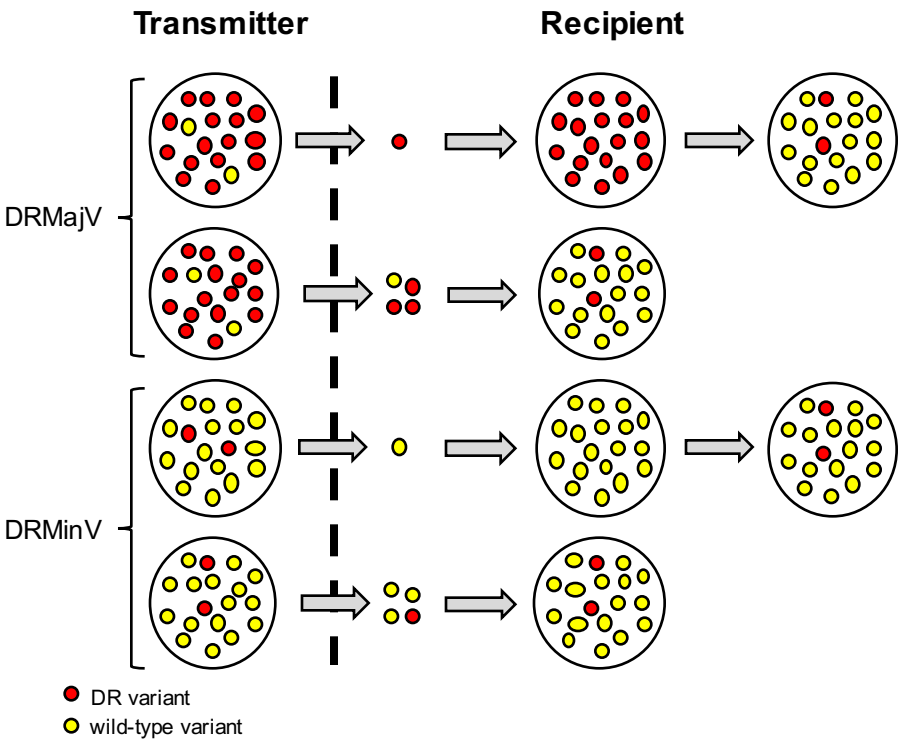
(PHE HIV in the UK 2014 Report; Cunningham *et al*., 2016)

Why is it important to determine the source of DRMinV in people recently infected?

- Transmission of MinV contradicts current understanding that most HIV infections arise from a single virus clone
- DRMinV selected under drug pressure are more likely to persist and compromise first-line therapy compared to naturally occurring variants
- Evidence for the transmission of DRMinV will assist in determining the utility of DRMinV detection and the clinical implications

(Ginella *et al*., 2011; Charpentier *et al*., 2015; Metzner *et al*., 2013; Cozzi-Lepri *et al*., 2015; Kyeyune *et al*., 2016; Li *et al*., 2013; Vandenhende *et al*., 2014; Johnson & Geretti, 2010; Derdeyn *et al*., 2004; Keele *et al*., 2008; Abrahams *et al*., 2009; Haaland *et al*., 2009)

Objective: Determine the source of DRMinV in people recently infected

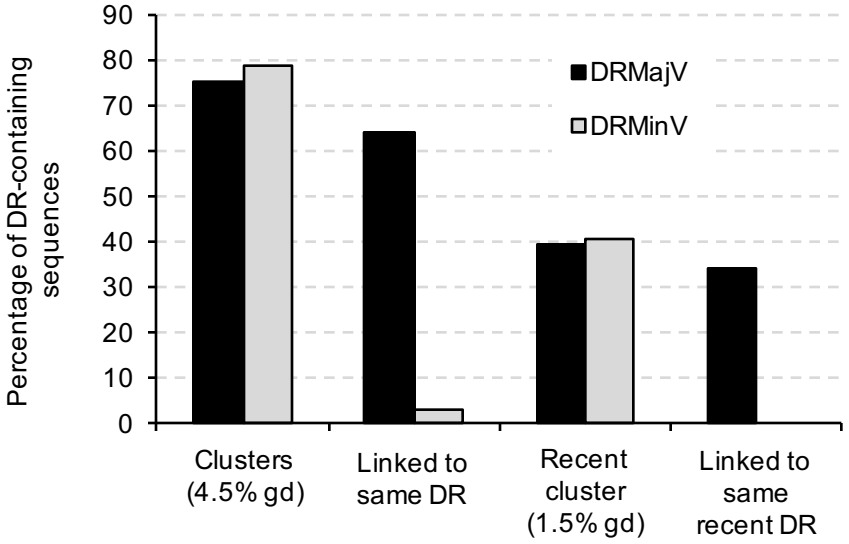


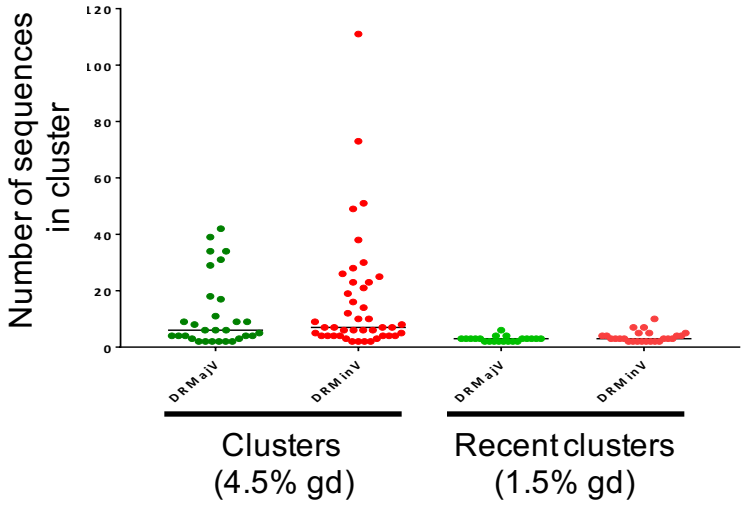
- Transmission of a single DRMajV followed by reversion to wild-type
- Transmission of mixed resistant and wild-type variants followed by decay of DR variant
- Transmission of a single wild-type variant followed by emergence of DRMinV by virus replication error
- Transmission of mixed resistant and wild-type variants followed by continued dominance of wild-type variant

Methods

- Used phylogenetic analysis to investigate the source of DRMinV in people recently infected
- Used the NGS data generated from recently infected MSM (*n=655*) and the Sanger data from UK HDRD (*n>100,000*)
- Performed transmission cluster analysis using Cluster Picker software to determine if sequences with DRMinV clustered with sequences with the same type of DRMajV
  - Using either 4.5% or 1.5% genetic distance (the latter to limit detection to recent transmission events); and 90% bootstrap support
- Investigated the effect of DRMinV on treatment outcome by linking to clinical outcome data from HARS and UK-CHIC databases
  - Virological failure defined as at least one report of a viral load above 200 or 1,000 cps/mL, 9+ months following initiation of ART

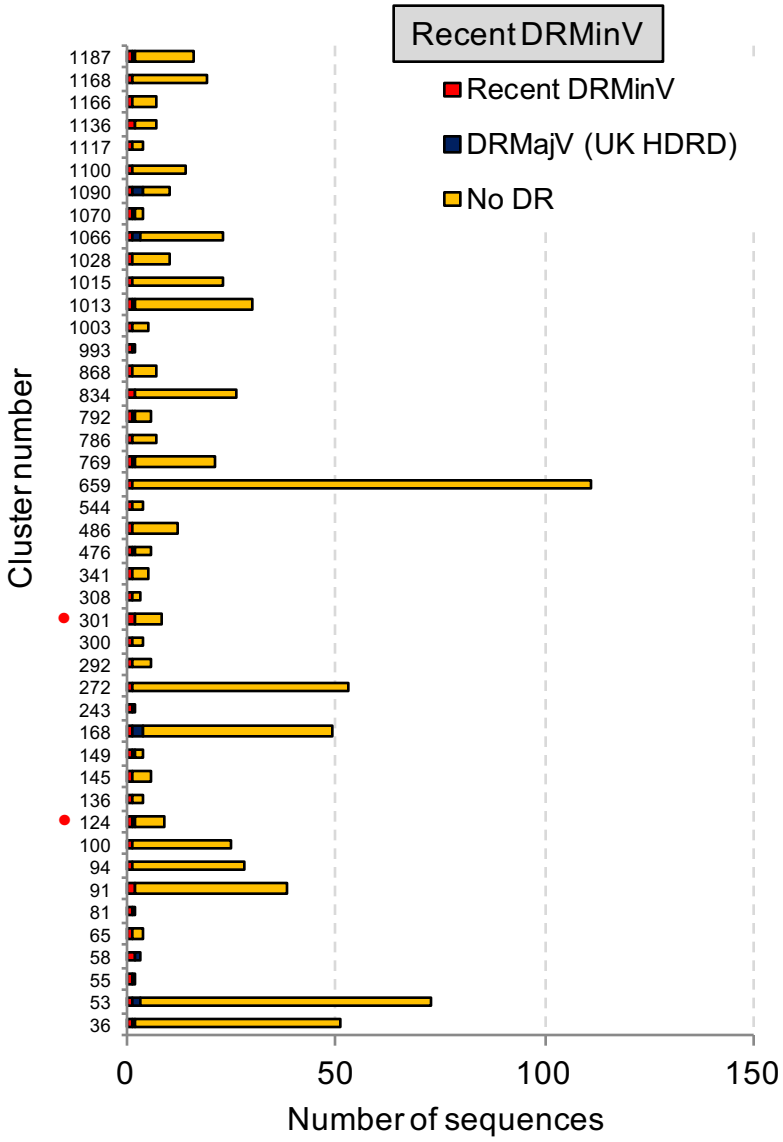
Results: No evidence of transmission of DRMinV



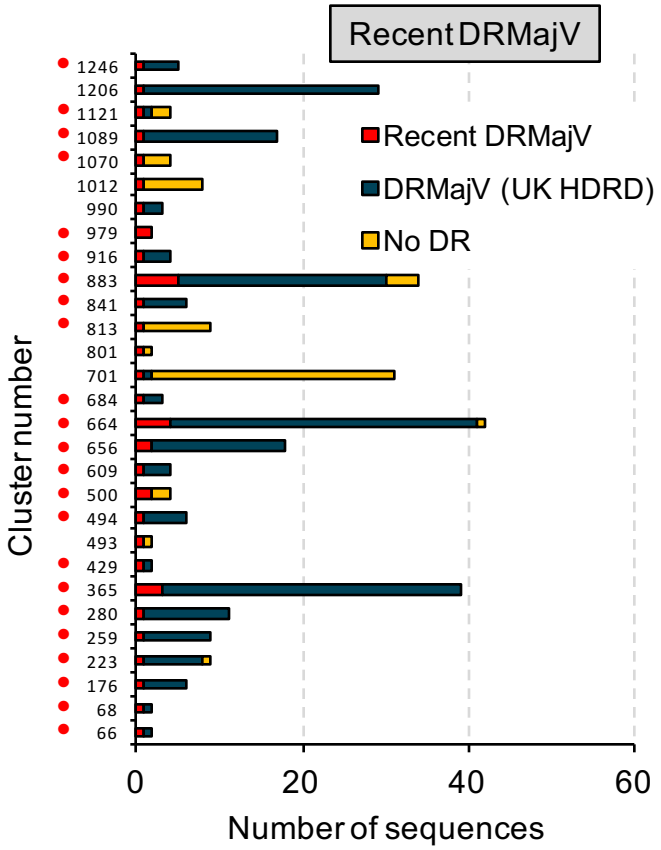


- 79% (48/61) of DRMinV and 76% (40/53) of DRMajV sequences were in clusters
- 64% (34/53) of DRMajV were in a cluster with sequence(s) containing the same DRM compared to 3% (2/61) of DRMinV sequences
- No evidence of recent transmission of DRMinV compared to 34% (18/53) for DRMajV sequences
- No significant difference in cluster sizes between DRMajV and DRMinV sequences

Results: Distribution of DR mutations in the clusters

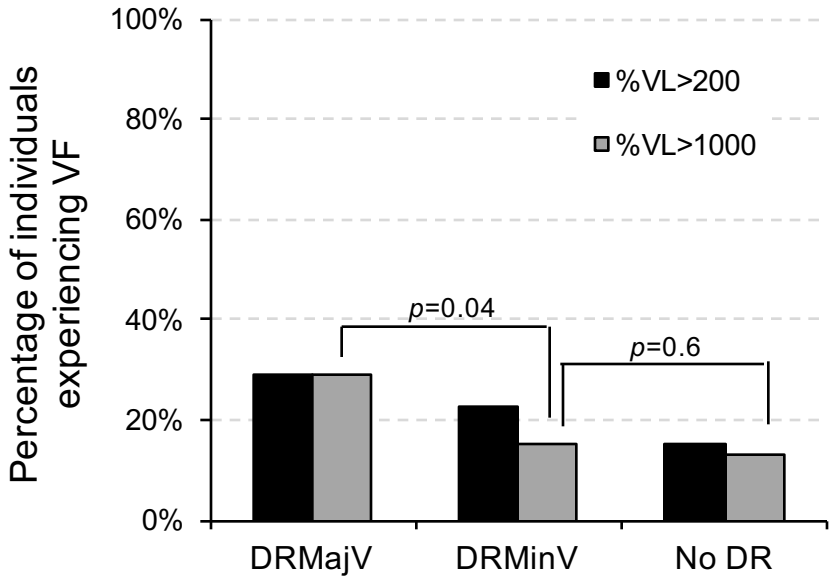


● Recent DR variant in cluster with sequence containing same DR variant



- Most recent DRMajV are present in a cluster with sequences containing the same DR variant
- Most recent DRMinV are present in a cluster with sequences containing no DR or containing a different DR variant

Results: Virological failure rate among recent MSM with DRMajV or DRMinV



- Virological failure rate among those harbouring DRMinV was similar to those with no DR at 15% (5/34) vs 12% (39/334) at VL>1,000 cps/mL
- In contrast, virological failure rate was 24% (8/33) among those harbouring DRMajV

Conclusions

- Using a densely sampled MSM population in the UK we show that there is no evidence that DRMinV are a result of a transmission event among recently infected MSM
- This finding does not rule out the possibility of DRMinV-to-DRMinV transmission in recently infected
- Preliminary analyses show that the presence of DRMinV had no significant impact upon the virological failure rate
- This suggests that the detection of DRMinV to inform first-line treatment options in people recently infected is unlikely to be of significant clinical benefit

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UKHIV Drug Resistance Database

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