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

- >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

- 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.
Acknowledgements

**Antiviral Unit (AVU)**
- Emma Cunningham
- Yuen Chan
- Carmen Manso
- Adriana Alvarez
- Jennifer Toswill
- Pat Cane

**Bioinformatics**
- Kieren Lythgow

**Clinical Services Unit (CSU)**
- Samuel Moses

**Centre for Infectious Disease Surveillance and Control (CIDSC)**
- Adamma Aghaizu

- Deenan Pillay (UCL & AHRI)
- Anna Maria Geretti (University of Liverpool)
- Stephane Hue (LSHTM)
- UK-HDRD & UK-CHIC Steering Committee members and Contributing Centers