



UK Health  
Security  
Agency

# The application of genomics in the clinical management and public health surveillance of HIV and HCV in the UK

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# UK Health Security Agency

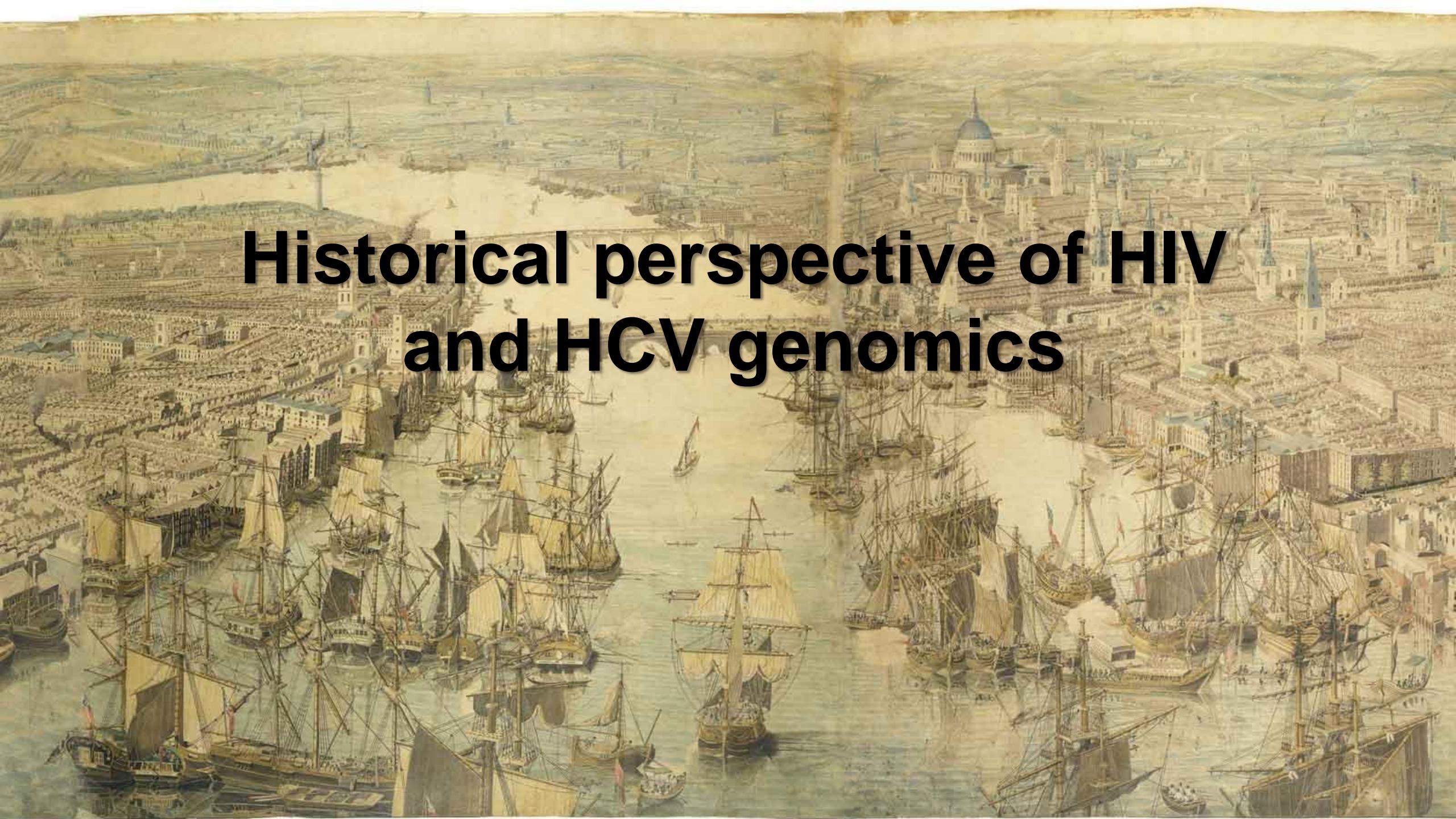


- Our mission is to prepare for, prevent and respond to health threats, save lives and protect livelihoods
- We are a centre of scientific and operational excellence in health protection. Our reach is local, national and global and we strive to improve health security worldwide.
- The threats we protect against range in type, scale and intensity, covering infectious disease – from pandemics to everyday infections – and environmental threats including radiation, chemical, nuclear and extreme weather events

# Antiviral Unit at UKHSA

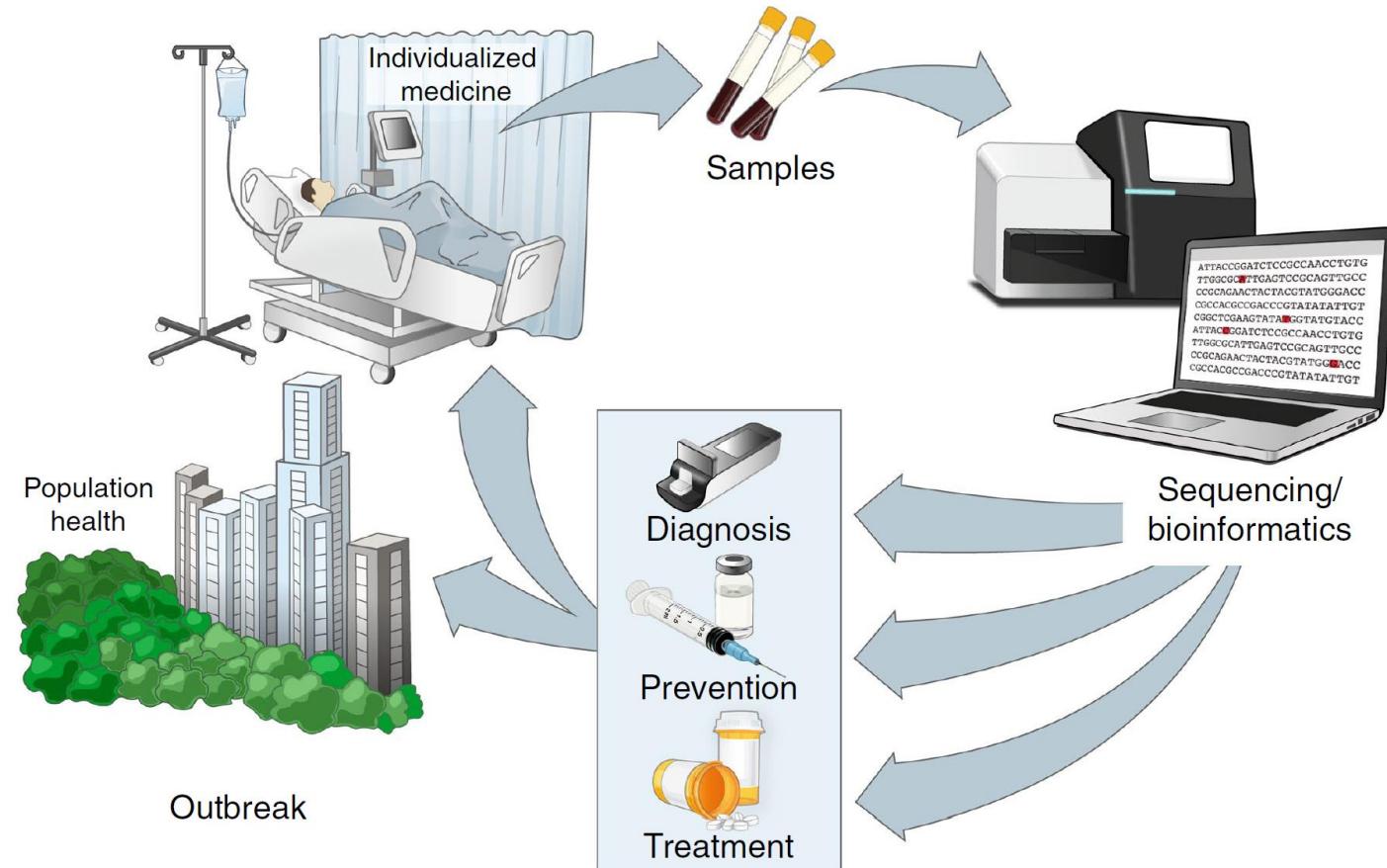
- National Reference Laboratory and WHO Global Specialised HIV Drug Resistance Laboratory
- UKAS accredited laboratory that performs antiviral resistance testing for direct patient care:
  - HIV – partial genome sequencing for PR, RT, IN and env using Sanger sequencing and occasionally NGS
  - HCV – whole genome sequencing using sequence capture and Illumina technology
  - HSV – partial genome sequencing for TK, DNAPol, UL5 and UL54 using Sanger sequencing and occasionally NGS
- Co-ordinate the UK HIV Resistance Network and host the UK HIV Drug Resistance Database
- Surveillance and research

- I. Past: historical perspective**
- II. Present: current situation**
- III. Future: vision**

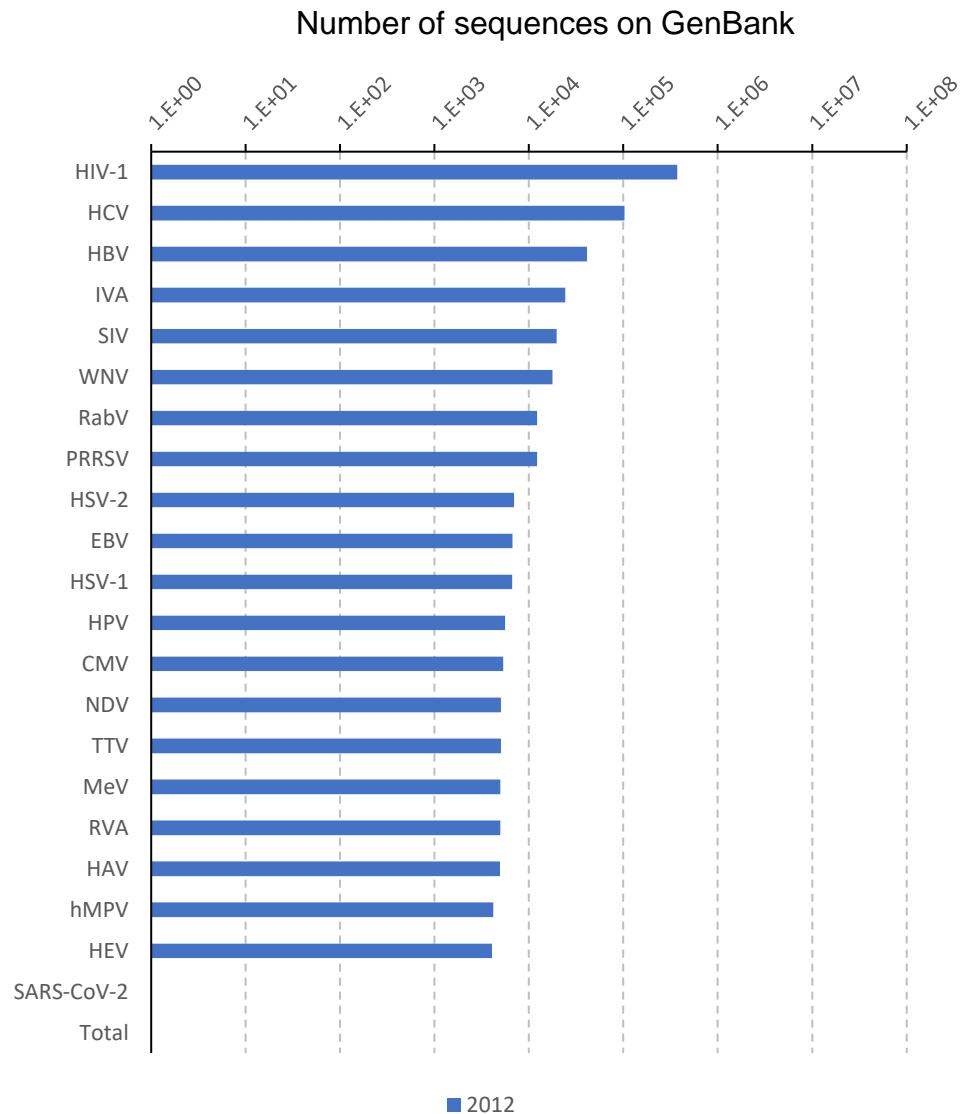
A detailed historical painting of a bustling port city, possibly London, during the 17th or 18th century. The foreground is filled with a variety of sailing ships, from small fishing boats to large three-masted商船. The middle ground shows the wide River Thames flowing through the city. In the background, a dense grid of buildings, including St. Paul's Cathedral with its iconic dome, stretches across the horizon under a clear sky.

# Historical perspective of HIV and HCV genomics

# Pathogen genomics revolution

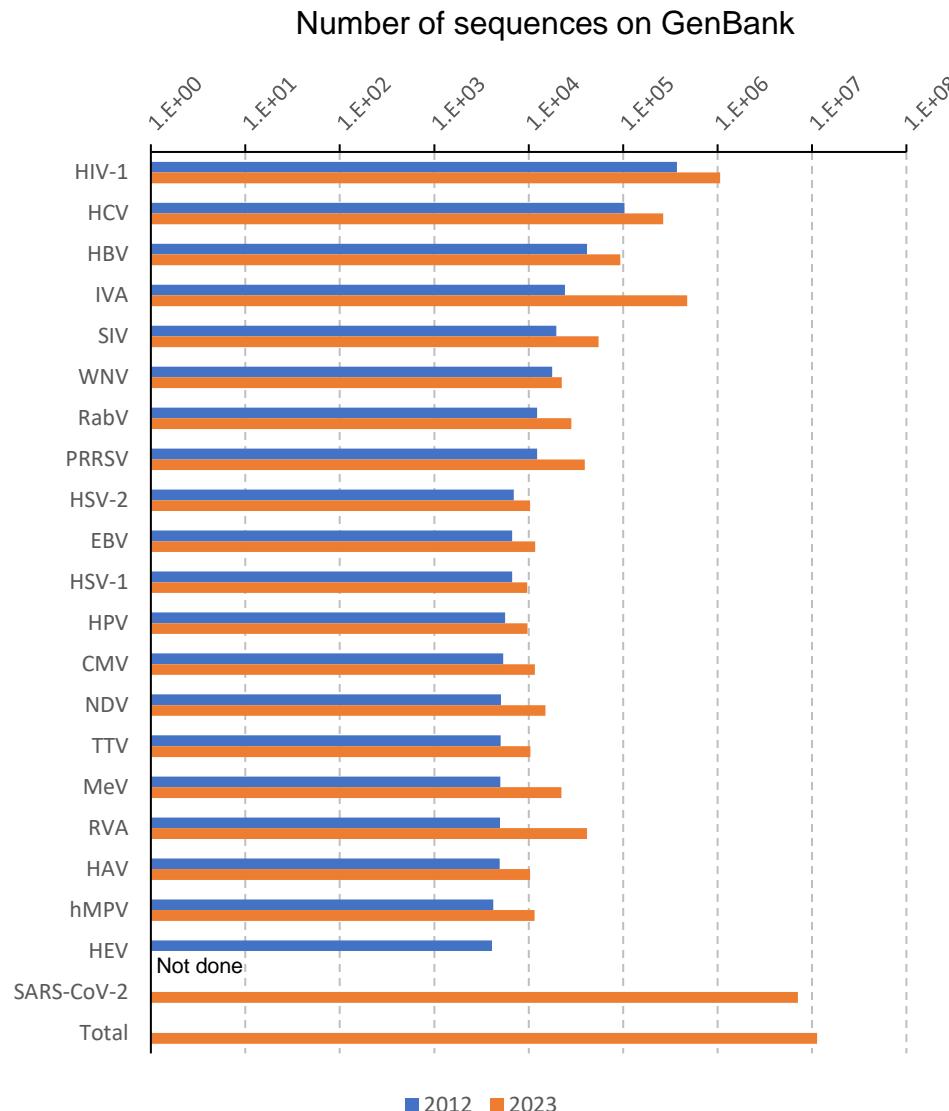


# HIV and HCV – most sequenced viruses...



- **Requirement for genotyping in the clinical pathway**
- **HIV** – genotyping is recommended by clinical guidelines to detect the presence of ARV resistance at baseline and treatment failure
- **HCV** – genotype is an important prognostic indicator and is used to inform therapy options and/or detect antiviral resistance

# HIV and HCV – most sequenced viruses...



...until the COVID pandemic came along

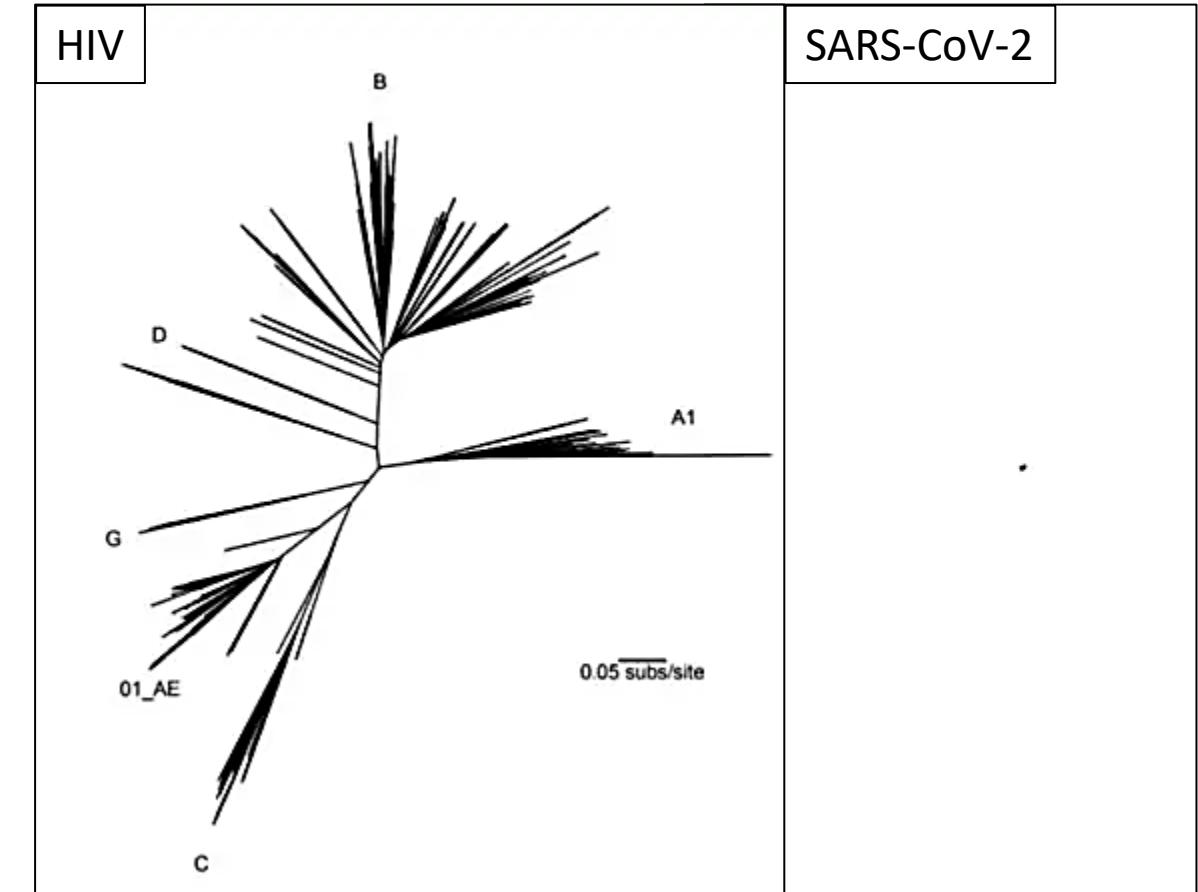
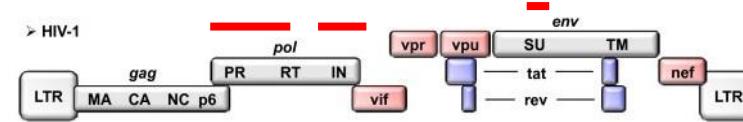
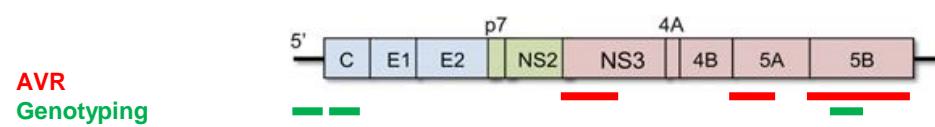


HIV



SARS-Cov2

# Challenges posed by HCV and (HIV) genetic diversity on sequencing



Ray SC and Thomas DL. PPID 7<sup>th</sup> ed, Chapter 154 2009

# HCV WGS by Sequence Capture

A genotype-agnostic assay: combines genotype + AVR into a single test



1. High-throughput extraction
  - EasyMAG
2. Metagenomic RNA library prep
  - Extensively modified in-house to accept ultra low viral RNA inputs
3. HCV-specific sequence-capture
  - In-house probe set design recently updated to capture new genotypes
4. MiSeq sequencing
  - Up to 62 samples, plus 10 controls
5. Bioinformatic pipeline
  - Technical reports
  - Clinical reports



Journal of  
Clinical Microbiology



## Comparison of Next-Generation Sequencing Technologies for Comprehensive Assessment of Full-Length Hepatitis C Viral Genomes

Emma Thomson,<sup>a</sup> Camilla L. C. Ip,<sup>b</sup> Anjna Badhan,<sup>d</sup> Mette T. Christiansen,<sup>a</sup> Walt Adamson,<sup>a</sup> M. Azim Ansari,<sup>c</sup> David Bibby,<sup>d</sup> Judith Breuer,<sup>a</sup> Anthony Brown,<sup>c</sup> Rory Bowden,<sup>b</sup> Josie Bryant,<sup>a</sup> David Bonsall,<sup>c</sup> Ana Da Silva Filipe,<sup>a</sup> Chris Hinds,<sup>a</sup> Emma Hudson,<sup>c</sup> Paul Klennerman,<sup>c</sup> Kieren Lythgow,<sup>d</sup> Jean L. Mbisa,<sup>d</sup> John McLauchlan,<sup>a</sup> Richard Myers,<sup>a</sup> Paolo Piazza,<sup>b</sup> Sunando Roy,<sup>e</sup> Amy Trebes,<sup>b</sup> Vattipally B. Sreenu,<sup>a</sup> Jeroen Witteveldt,<sup>f</sup> STOP-HCV Consortium, Eleanor Barnes,<sup>c</sup> Peter Simmonds,<sup>c</sup>

MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom<sup>a</sup>; Oxford Genomics Centre, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom<sup>b</sup>; Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom<sup>c</sup>; Virus Reference Department, Public Health England, London, United Kingdom<sup>d</sup>; University College London (UCL), Division of Infection and Immunity, London, United Kingdom<sup>e</sup>; Roslin Institute, University of Edinburgh, Edinburgh, United Kingdom<sup>f</sup>



METHODS  
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## Technical Validation of a Hepatitis C Virus Whole Genome Sequencing Assay for Detection of Genotype and Antiviral Resistance in the Clinical Pathway

OPEN ACCESS

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Original article

Clinical evaluation of a Hepatitis C Virus whole-genome sequencing pipeline for genotyping and resistance testing

Daniel Bradshaw<sup>a</sup>, David F. Bibby, Carmen F. Manso, Renata Piorkowska, Hodan Mohamed, Juan Ledesma, Laura Bubba, Yuen T. Chan, Siew Lin Ngui, Simon Carne, Jean L. Mbisa, the STOP-HCV Consortium

National Infection Service, Public Health England, London, UK

# Genotypic Interpretation Systems (for antiviral resistance)

■ [hcv.glue.cvr.ac.uk](http://hcv.glue.cvr.ac.uk)

HCV-GLUE Home Sequence Data Drug Resistance Analys... Offline version About

**HCV-GLUE**  
A Sequence Data Resource for Hepatitis C Virus

Hepatitis C virus (HCV) affects over 100 million people worldwide and can lead to liver disease and occasionally cirrhosis. While direct-acting antiviral drugs (DAAs) have improved treatment prospects for HCV significantly, drug resistance has emerged both *in vitro* and in clinical trials. HCV exhibits a high level of genetic variation and so there is a need for computational resources to organise and analyse existing and new HCV sequence data in research, public health and clinical contexts.

HCV-GLUE is a bioinformatics resource for HCV sequence data. The web version can be used for basic analysis. An offline version of the resource can be installed by bioinformaticians and used for more advanced work.

**Web site highlights**

- A database of HCV sequences and metadata from NCBI, updated daily and arranged into clades (genotypes, subtypes).
- Pre-built multiple-sequence alignments of NCBI sequences, which may be downloaded in user-defined sections.
- A database of DAA-resistant polymorphisms, developed in collaboration with the Virus Reference Department at Public Health England.
- An analysis tool providing genotyping, drug resistance analysis and visualisation of submitted FASTA sequences (example generated report).

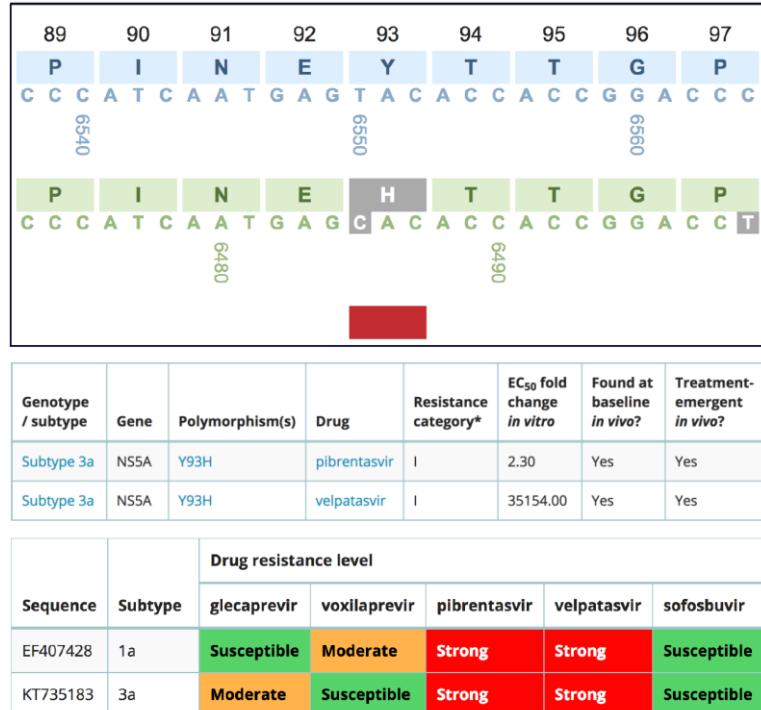
**Offline version**

The offline version of HCV-GLUE includes all features of the web version plus:

- A rich set of bioinformatic functions for exploring the dataset.
- Tools for the analysis of NGS sequences (SAM/BAM files) including drug resistance analysis (example generated report).

HCV-GLUE is based on the GLUE software framework. GLUE and HCV-GLUE are developed by the MRC University of Glasgow Centre for Virus Research. The drug resistance evidence base is collated by the Public Health England Virus Reference Department in concert with colleagues from the UK HCV research community.  
Please note this is beta software, still undergoing development and testing before its official release.



**STANFORD UNIVERSITY HIV DRUG RESISTANCE DATABASE**  
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM

**HIVdb: Genotypic Resistance Interpretation Algorithm**

**Summary Data**

Sequence includes PR: codons: 1 - 99  
Sequence includes RT: codons: 1 - 341  
There are no insertions or deletions  
Subtype and % similarity to closest reference isolate:  
1 PR: CRF02\_AG (98.3%)  
2 RT: CRF02\_AG (95.4%)

**Drug Resistance Interpretation**

PI Major Resistance Mutations: None  
PI Minor Resistance Mutations: None  
Other Mutations:  
I13V, K14R, I15L, K20I, E36D, M36I, R41K, H69K, L89M

**Protease Inhibitors**

ATV Susceptible  
DRV Susceptible  
FPV Susceptible  
IDV Susceptible  
LPV Susceptible  
NFV Susceptible  
SQV Susceptible  
TPV Susceptible

**PR Comments**

- The following 3 of the 21 tipranavir RESIST study mutations were present: I13V, M36I, H69K (Baxter J et al., 2010).
- I13V is a common polymorphism that is slightly more common in treated compared with untreated subtype B isolates. In subtypes A, AE, AG, and G it is the consensus residue. I13V was weakly associated with decreased virological response to TPV in the RESIST trials.
- K20R/M1/I1 are weakly associated with resistance to each of the PIs when present with other mutations. Many variants at this position occur commonly in non-subtype B viruses.
- M36I/V are weakly associated with PI resistance when present with other mutations. M36I occurs commonly in certain non-subtype B viruses. M36LT are rare variants of uncertain significance.
- H69K is a highly polymorphic residue that was weakly associated with a decreased virologic response to TPV in the RESIST trials.

**Drug Resistance Interpretation**

NRTI Resistance Mutations: M41L, M184V, T215Y  
NNRTI Resistance Mutations: None  
Other Mutations:  
V95T, T90A, D123E, I136V, S162T, K173T, Q174K, D177E, T200A, Q207E, V245Q, T286A, E291D, V292I, I293V, P294V, S322A, I326V, Q334P, G335D

**Nucleoside RTI** **Non-Nucleoside RTI**

Sequence	Subtype	glecaprevir	voxilaprevir	pibrentasvir	velpatasvir	sofosbuvir
EF407428	1a	Susceptible	Moderate	Strong	Strong	Susceptible
KT735183	3a	Moderate	Susceptible	Strong	Strong	Susceptible

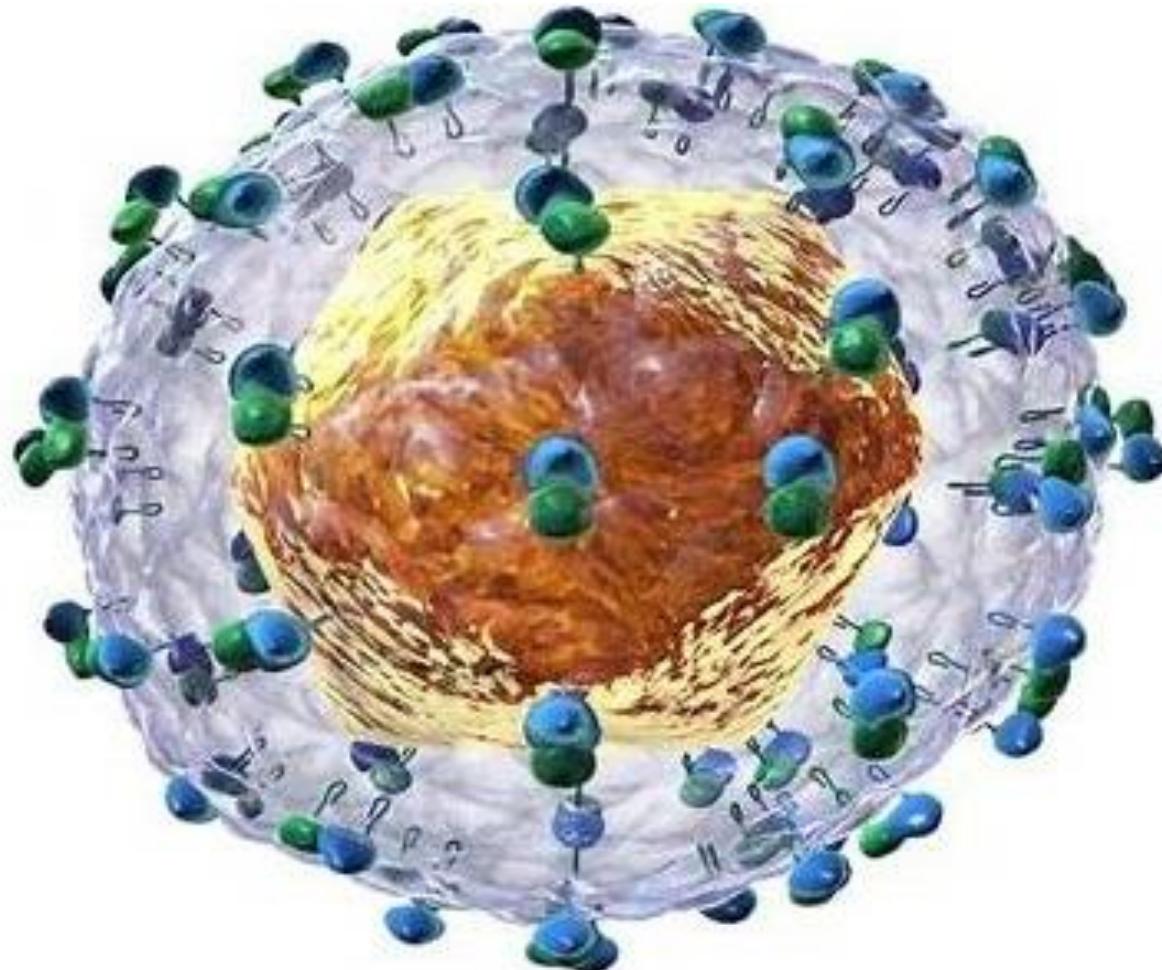
**RT Comments**

- M41L usually occurs with T215Y. Together these mutations confer intermediate-to-high level resistance to AZT and d4T and a lower level of resistance to ddI, ABC, and TDF.
- M184V/I cause high-level *in vitro* resistance to 3TC and FTC and low-level *in vitro* resistance to ddI and ABC. M184V/I increase susceptibility to AZT, TDF, and d4T.
- T215Y causes AZT and D4T resistance and reduces susceptibility to ABC, ddI, and TDF particularly when it occurs in combination with M41L and L210W.
- M184V partially reverses AZT, d4T, and TDF resistance caused by other AZT mutations (TAMs). AZT mutations in this isolate include: M41L, T215Y.
- M184V partially reverses AZT, d4T, and TDF resistance caused by other AZT mutations (TAMs). AZT mutations in this isolate include: M41L, T215Y.

The background image is a wide-angle aerial photograph of the London skyline at dusk or night. The River Thames flows through the center, with the illuminated Tower Bridge spanning it. The City of London is visible in the background, and the surrounding residential and commercial areas are lit up with city lights. The overall atmosphere is vibrant and modern.

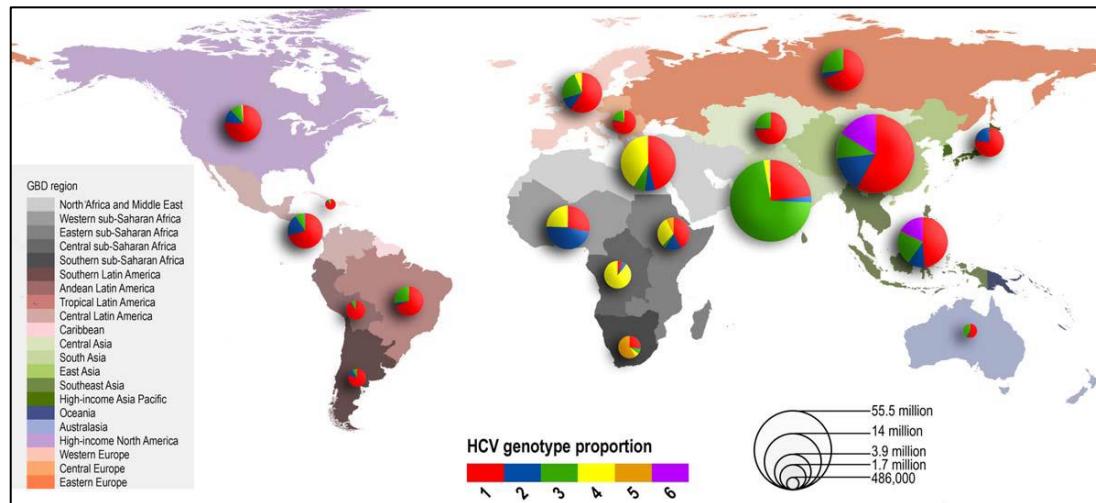
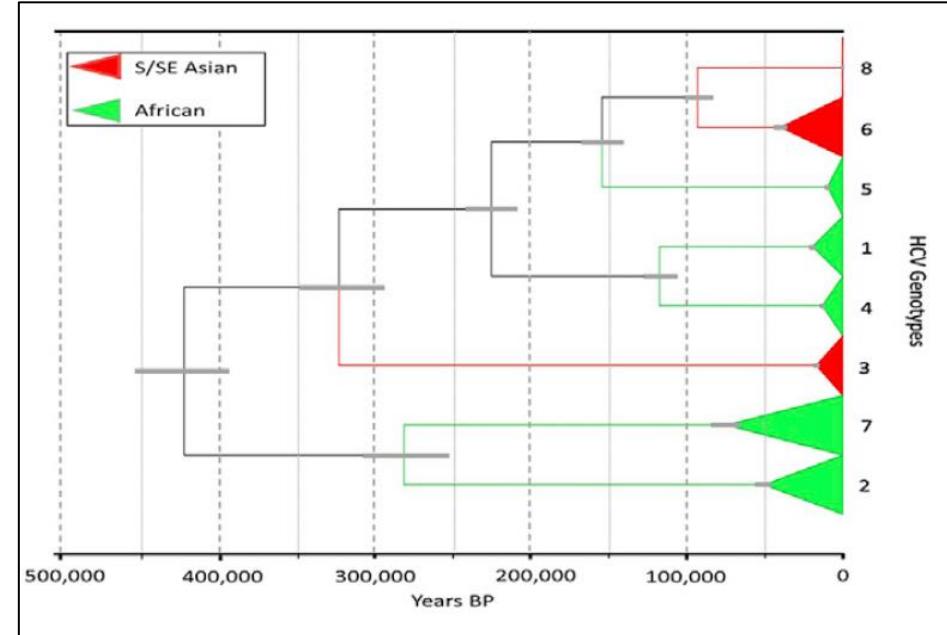
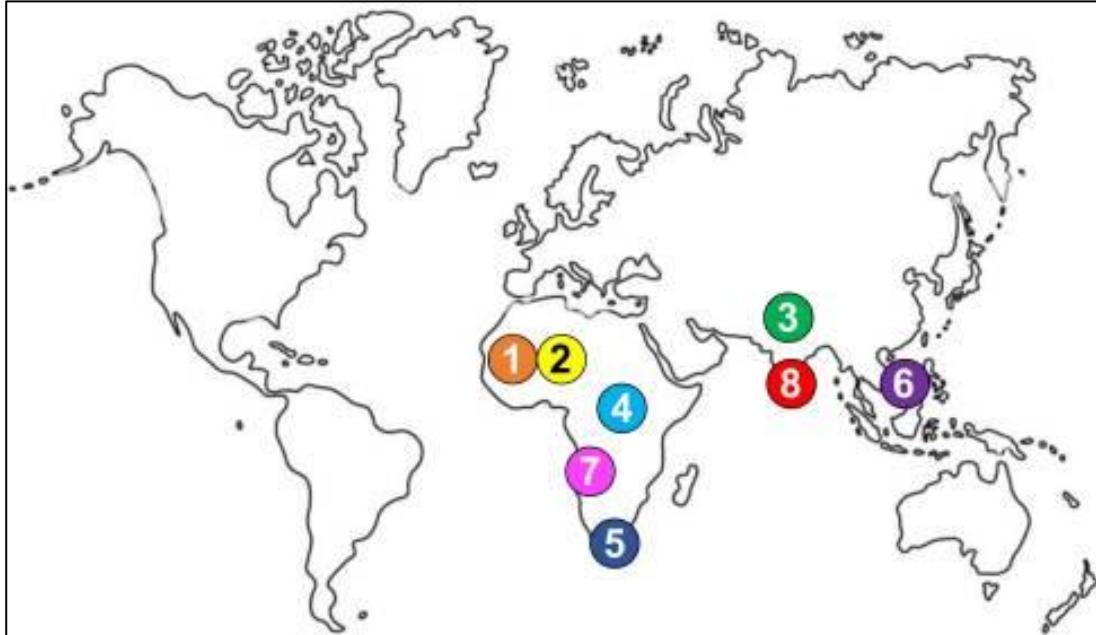
# Current applications of HIV and HCV genomics in the UK

# Hepatitis C Virus (HCV)



- **Genotyping to inform treatment options:** Endemic subtypes treatment outcomes study
- **Virus characterization:** Identification of novel variants
- **Outbreak investigation:** Tracking of transmissions clusters

# HCV genotypes: geographic distribution

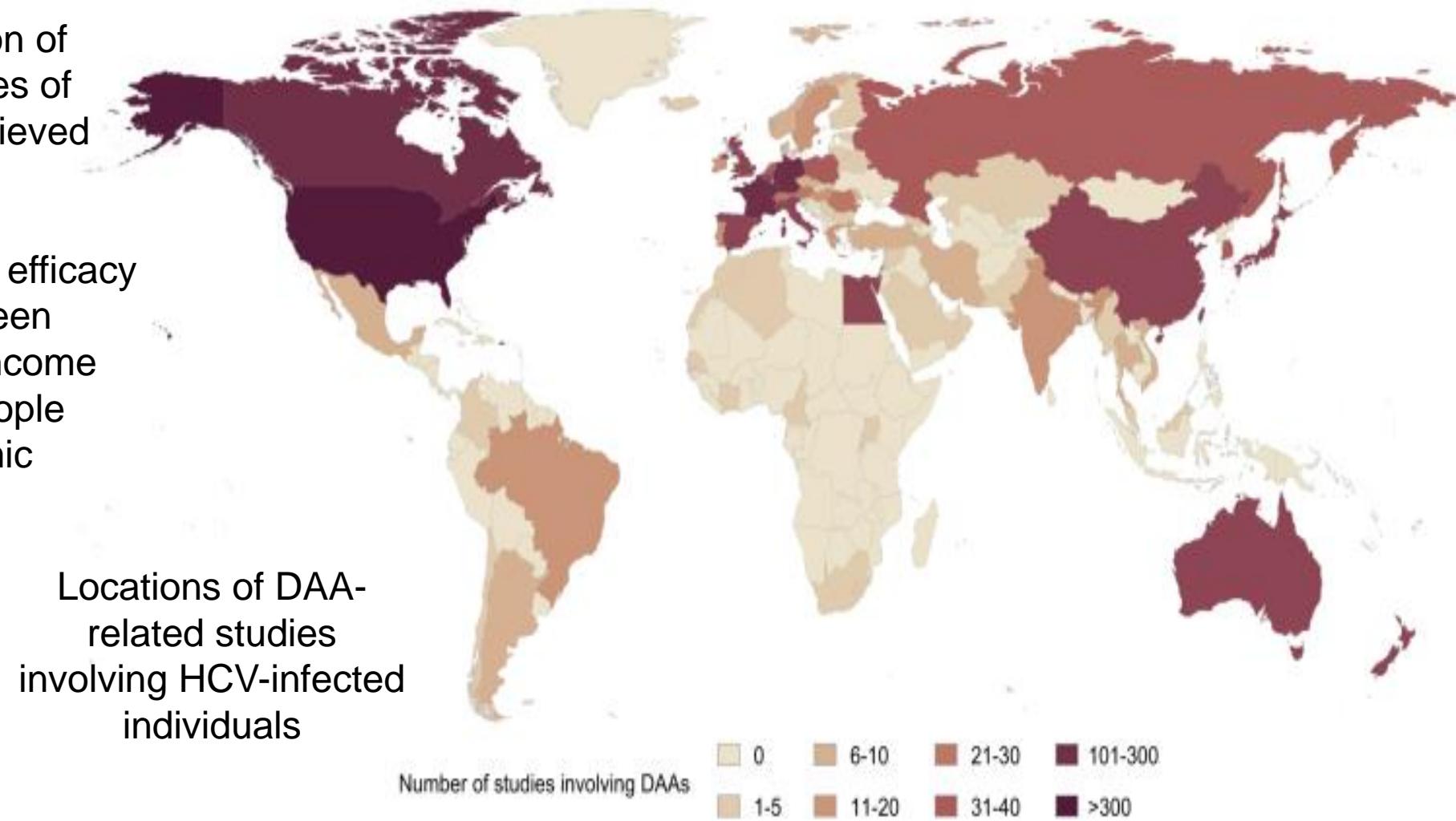


- 8 genotypes and ~100 subtypes
  - GT1a and 3a most common – epidemic subtypes
- Theories on origins of HCV from animal reservoir
  - Single introduction hundreds of thousands of years ago - 423,000 [394,000-454,000; 95%HPD]
  - Multiple jumps in different regions

(Vo-Quang & Pawlotsky, 2024 *Gut*; Messina et al., 2015 *Hepatology*; Ghafari et al., 2021 *Current Biology*)

# Clinical trials for DAA efficacy

- Since the introduction of DAAs, high cure rates of >95% are being achieved
- The majority of DAA efficacy clinical trials have been carried out in high-income countries among people infected with epidemic subtypes



# Treatment outcomes in endemic subtypes

- Single arm prospective study evaluating efficacy of LDV/SOF (SHARED study) - **subtype 4r** Sustained Virological Response at 12 weeks (SVR12) post treatment of **56%** vs 93% among other GT4 subtypes
- Phase 3 trial evaluating efficacy of SOF/VEL across 38 sites in Asia - **subtype 3b** SVR 12 of **76%** vs 95% in subtype 3a

(Gupta, et al. 2019 *Lancet Gastroenterol Hepatol*; Wei, et al. 2019 *Lancet Gastroenterol Hepatol*)

# Treatment outcomes in individuals infected with endemic HCV subtypes in England

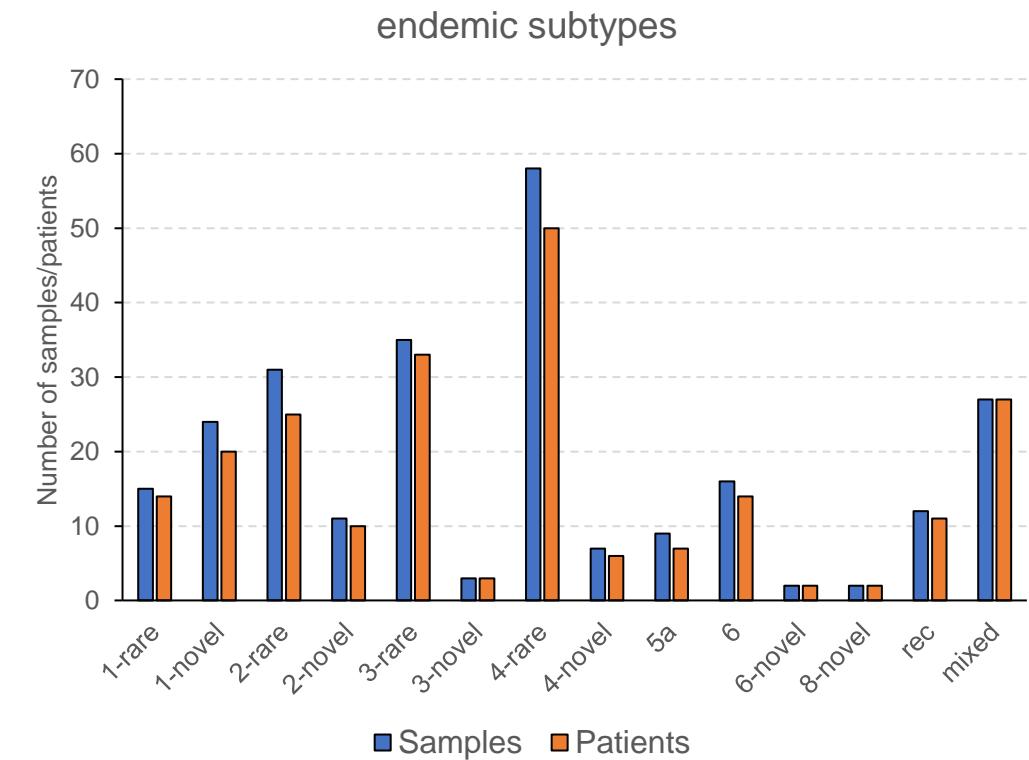
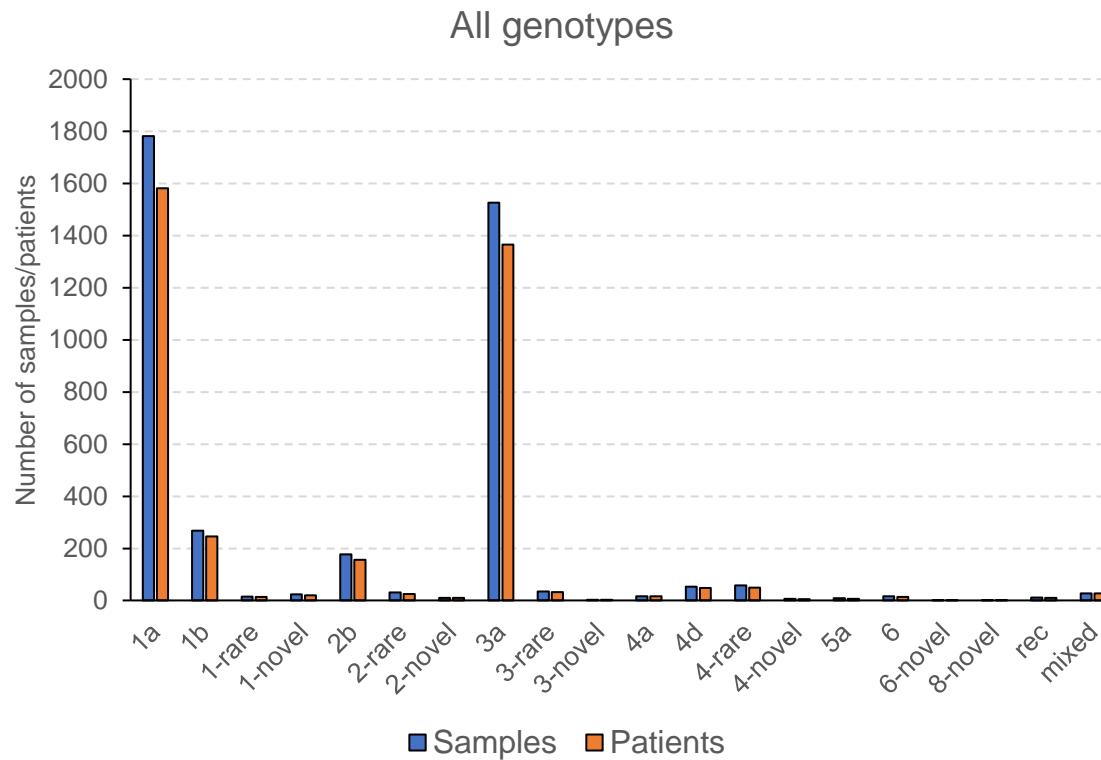
PhD student: **Laura Phillips**  
(Journal of Infection – *in press*)

# Endemic subtype surveillance programme

**Aim:** to investigate treatment outcomes in endemic subtypes in England

- HCV data routinely collected at the UKHSA as part of the NHS England treatment programme delivered by HCV Operational Delivery Networks (ODN)
  - Dataset includes demographic, clinical and epidemiological data
  - Antiviral Unit provides a WGS service for genotyping and antiviral resistance testing for informing clinical care
- Epidemic subtypes '**common**' to the UK: 1a, 1b, 3a, 4a
  - 2b and 4d not included as not routinely identified and recorded at subtype level
- Endemic subtypes '**rare**' to the UK, all other subtypes
  - additionally submitted for whole-genome sequencing to confirm subtype

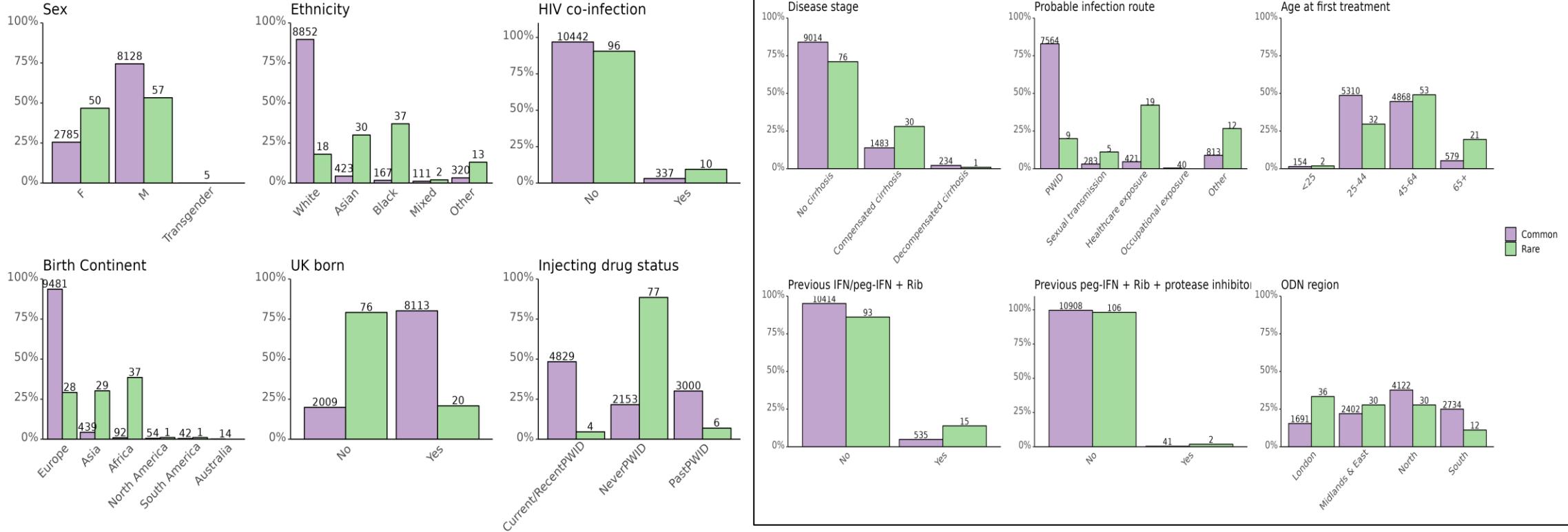
# UKHSA HCV WGS clinical service (Aug 2019 to Dec 2023)



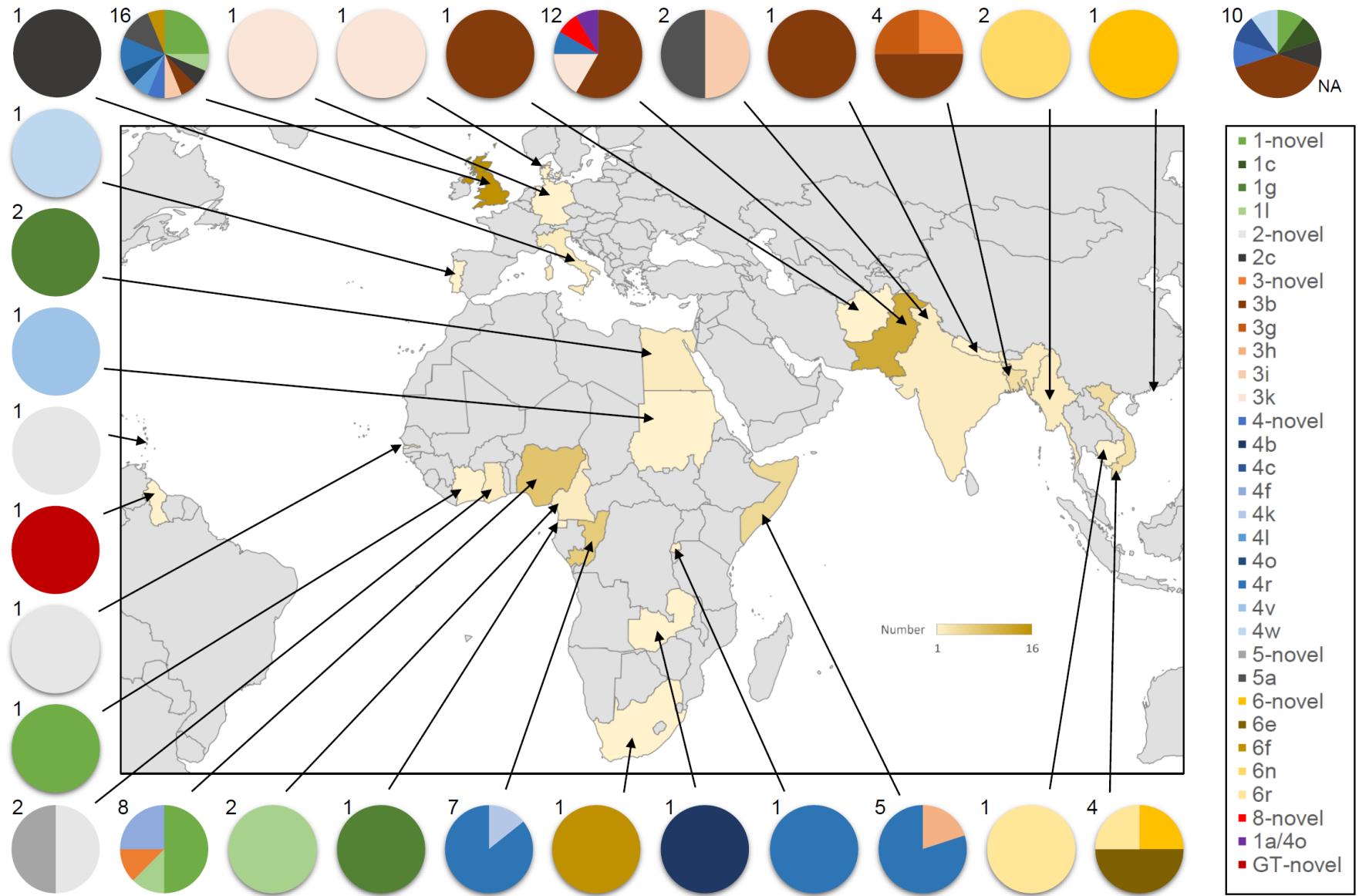
- Majority of samples tested are subtypes 1a and 3a (**epidemic subtypes**)

- 'Rare' (**endemic**) subtypes: other than 1a, 1b, 2b, 3a, 4a and 4d

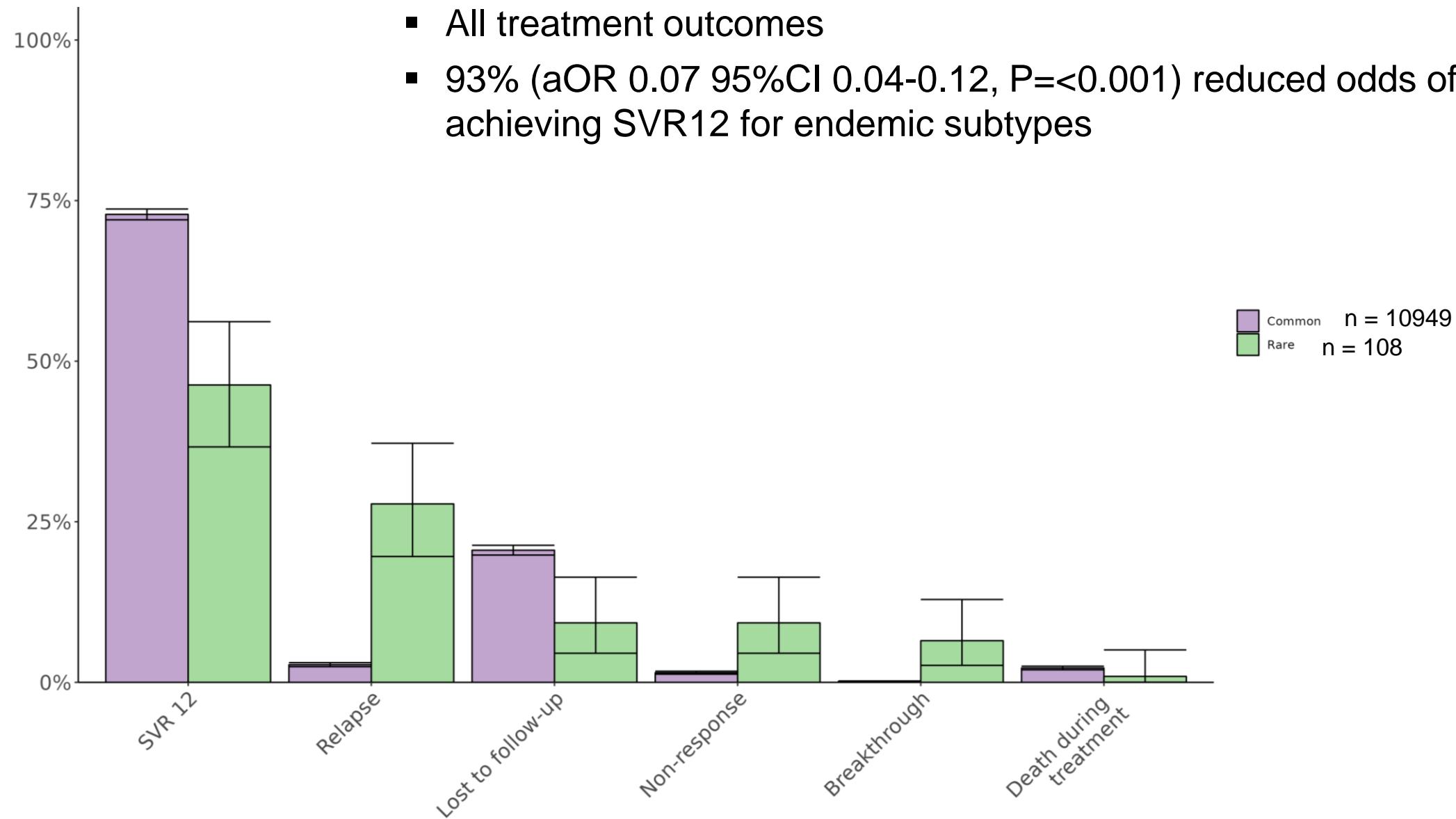
# Characteristics of study population



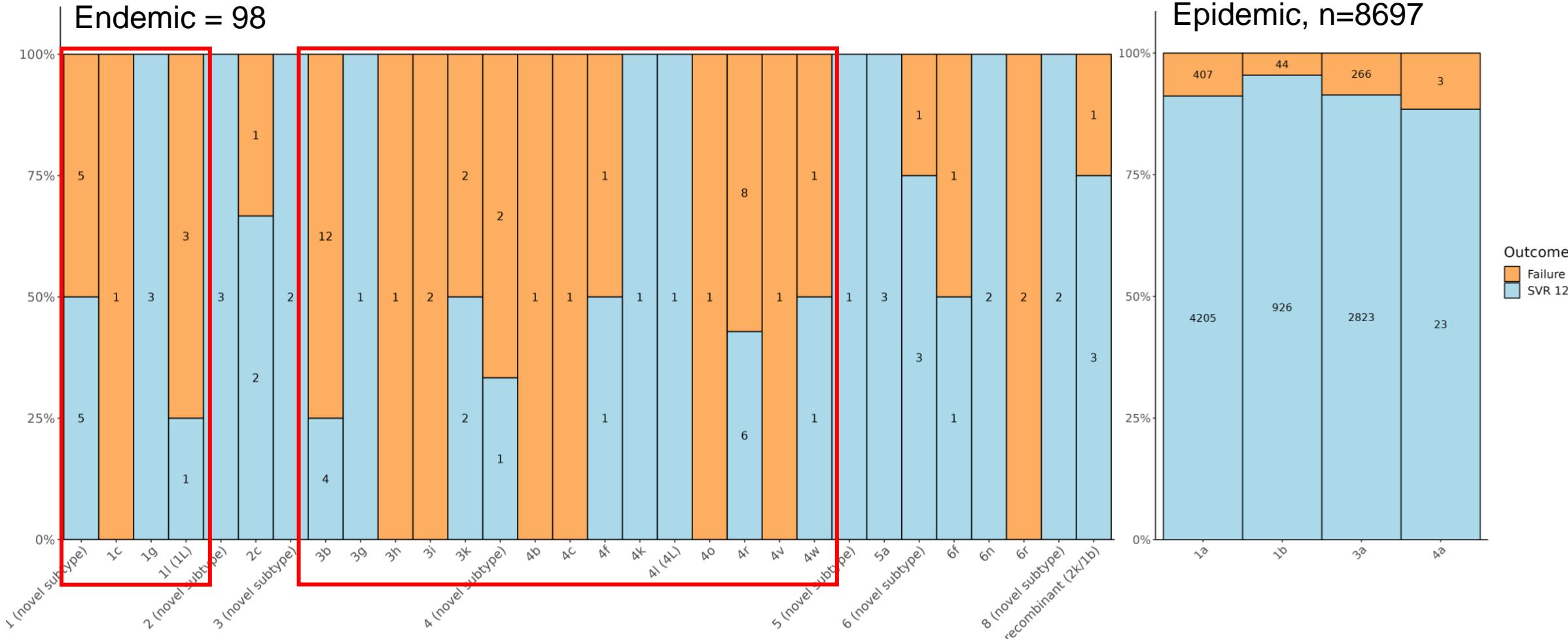
# Country of birth of people infected with endemic subtypes



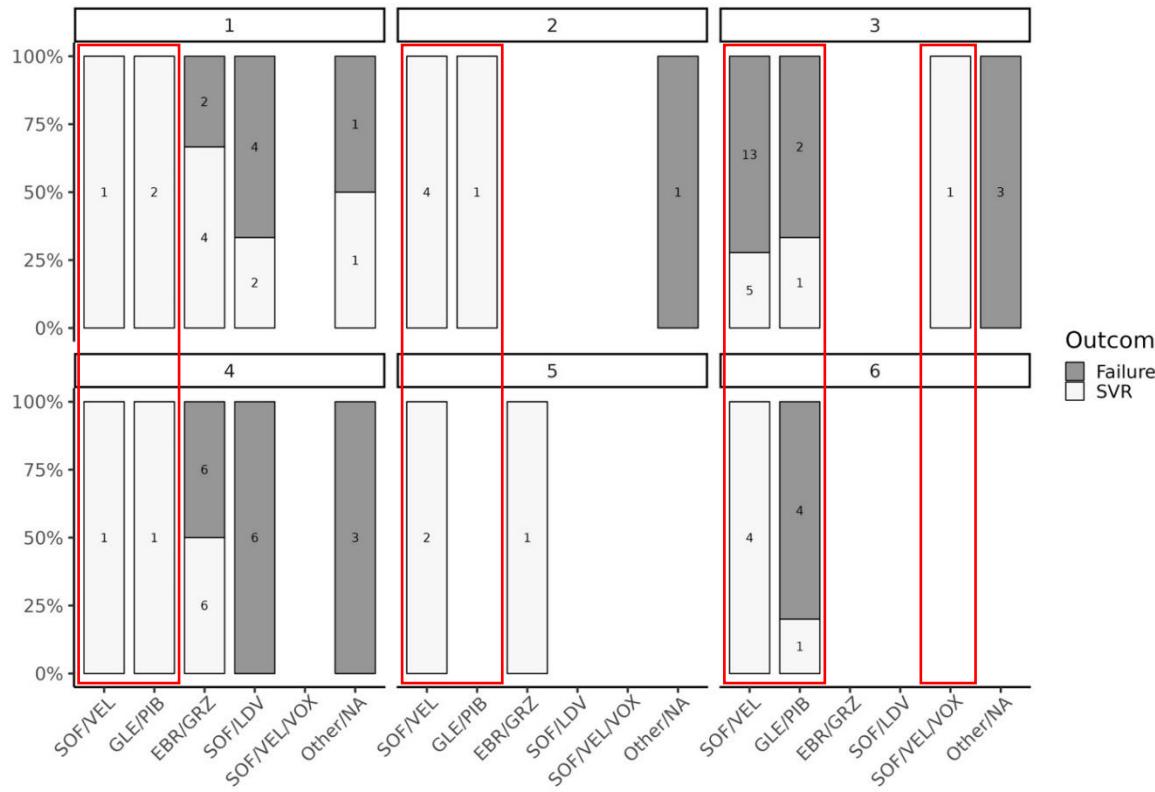
# Epidemic vs endemic subtypes treatment outcomes



# Treatment outcomes by subtype



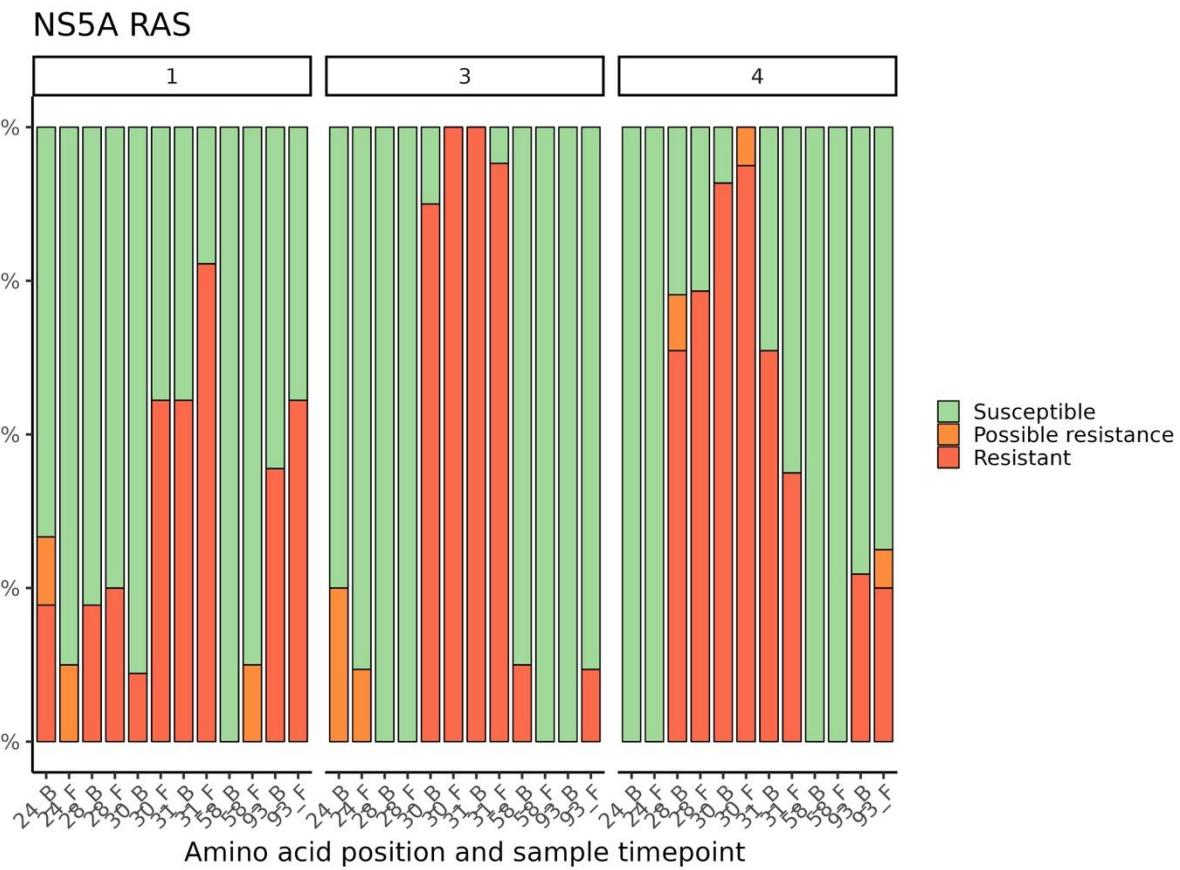
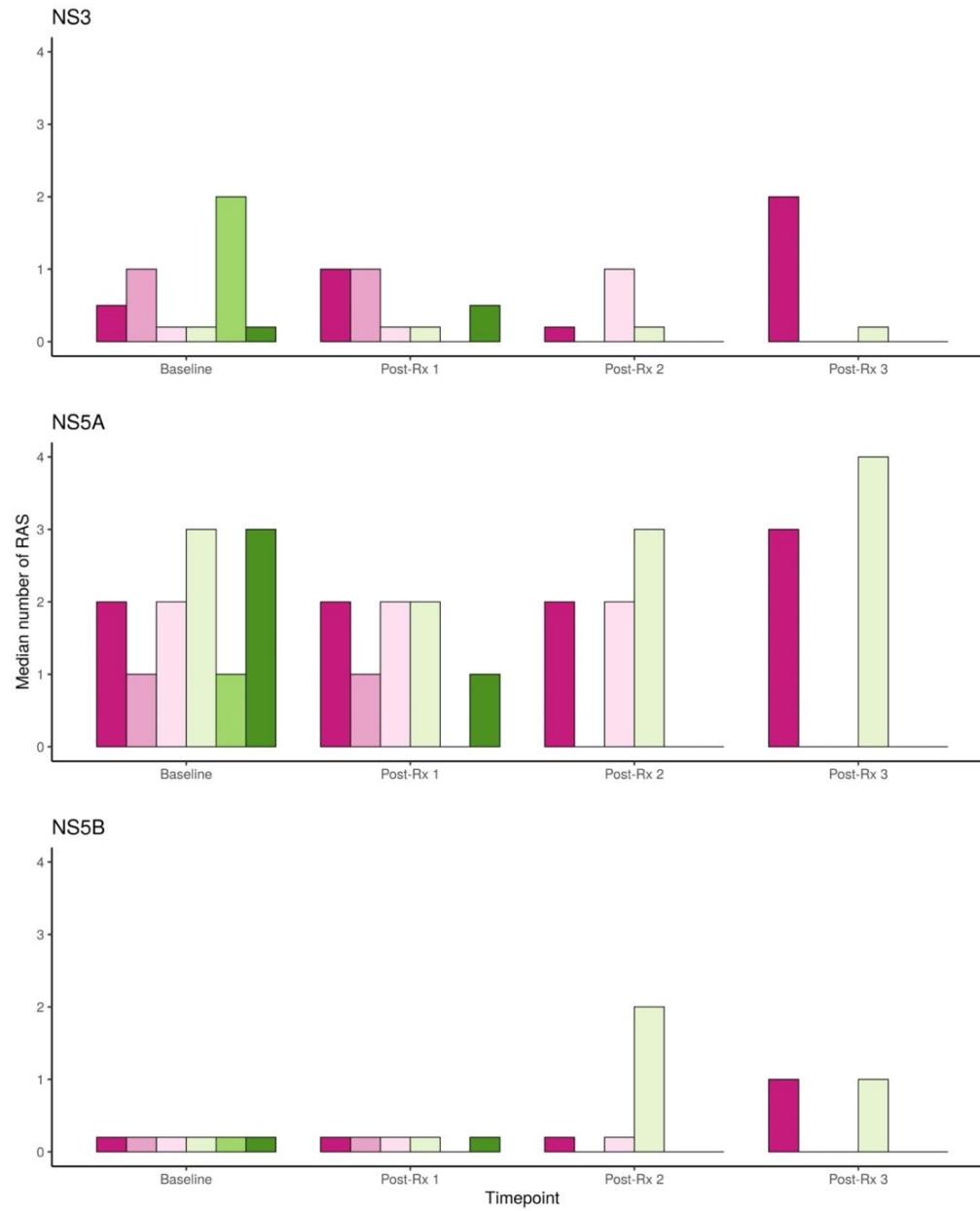
# Genotypic vs pangenotypic regimens



- Most endemic GT3 subtypes were 3b (n=16)
- SOF/VEL and GLE/PIB less successful
- Maybe triple therapy is the answer (SOF/VEL/VOX or SOF/GLE/PIB)
- Most endemic GT1 and 4 subtypes were 1-novel (n=10) or 4r (n=14)
- Genotypic regimens less successful
- Pangenotypic regimens more successful

NHSE 'rate card'	Genotypes	Treatment options	
	GT1 & 4	ELB/GRZ	SOF/LDV
	GT2, 3, 5 & 6	SOF/VEL	GLE/PIB

# Inherent NS5A resistance



(B=baseline; F=failure)

# Identification and characterisation of novel HCV variants

*The Journal of Infectious Diseases*

MAJOR ARTICLE

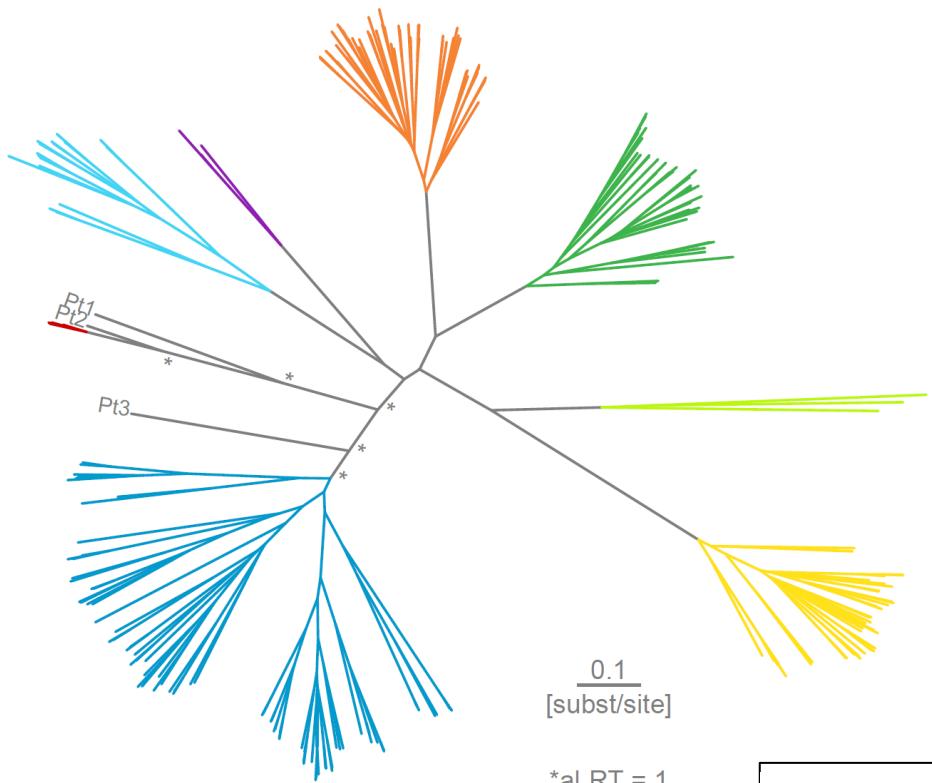


Identification of 2 Novel Subtypes of Hepatitis C Virus Genotype 8 and a Potential New Genotype Successfully Treated With Direct Acting Antivirals

Jean L. Mbisa,<sup>1,2,●</sup> Zena Lapp,<sup>3</sup> David F. Bibby,<sup>1</sup> Laura T. Phillips,<sup>1,2</sup> Carmen F. Manso,<sup>1</sup> Simon Packer,<sup>1</sup> Ruth Simmons,<sup>1,2</sup> Kathryn Harris,<sup>4</sup> Jaiganesh Mohan,<sup>5</sup> Lalitha Chinnappan,<sup>5</sup> Thomas Leitner,<sup>3</sup> and Daniel Bradshaw<sup>1,2</sup>

<sup>1</sup>Virus Reference Department, UK Health Security Agency, London, United Kingdom; <sup>2</sup>National Institute for Health and Care Research Health Protection Research Unit (NIHR HPRU) in Bloodborne and Sexually Transmitted Infections, London, United Kingdom; <sup>3</sup>Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, Los Alamos, New Mexico, USA; <sup>4</sup>Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; and <sup>5</sup>Warrington and Halton Teaching Hospitals NHS Foundation Trust, Warrington, United Kingdom

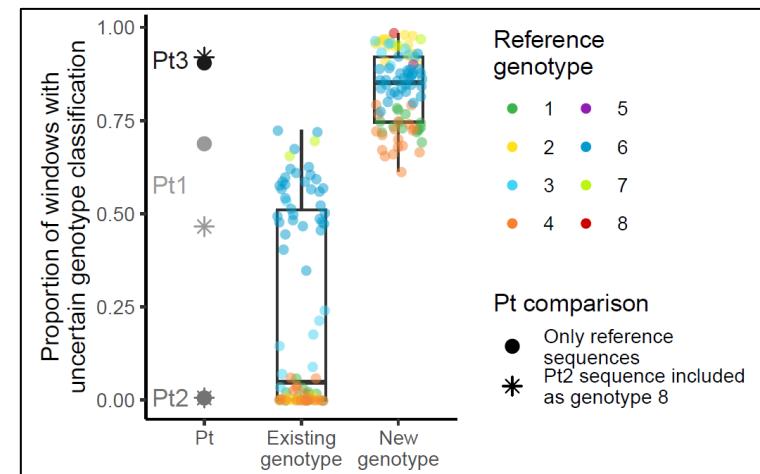
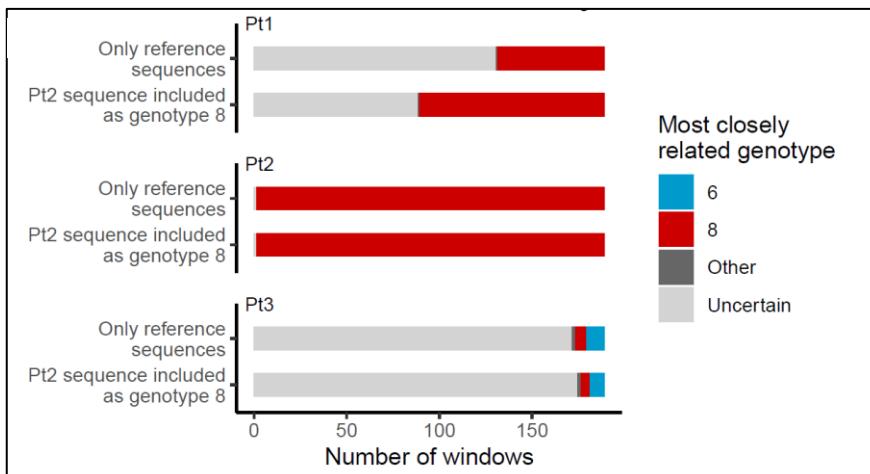
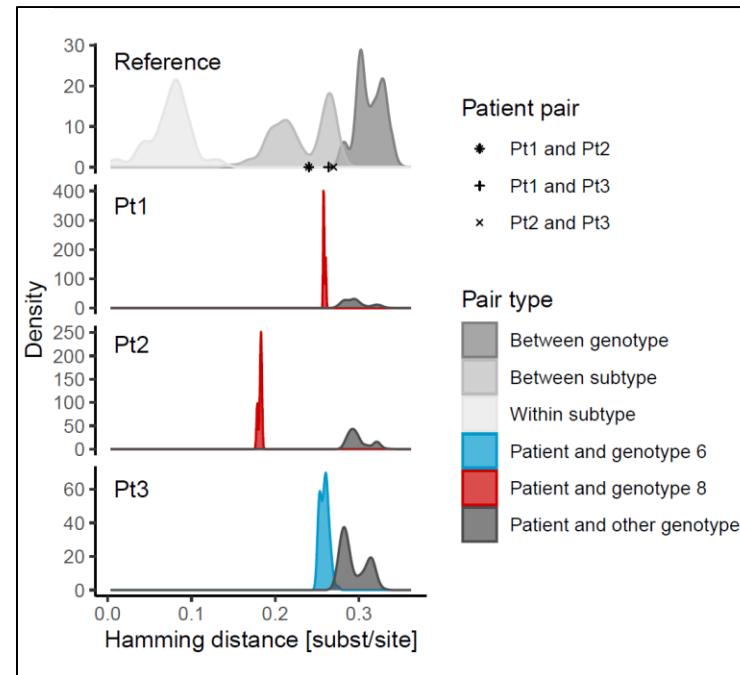
# Identification of new GT8 subtypes and new genotype



Patient (gender)	Country of birth	Ethnicity	Initial GT (assay)
Pt1 (M)	India (Kerala)	Asian	5a (LiPA)
Pt2 (F)	Pakistan	Asian	Untyped (NS5b sequencing)
Pt3 (F)	Guyana	Indo-Asian	1 – unspecified subtype (NS5b sequencing)

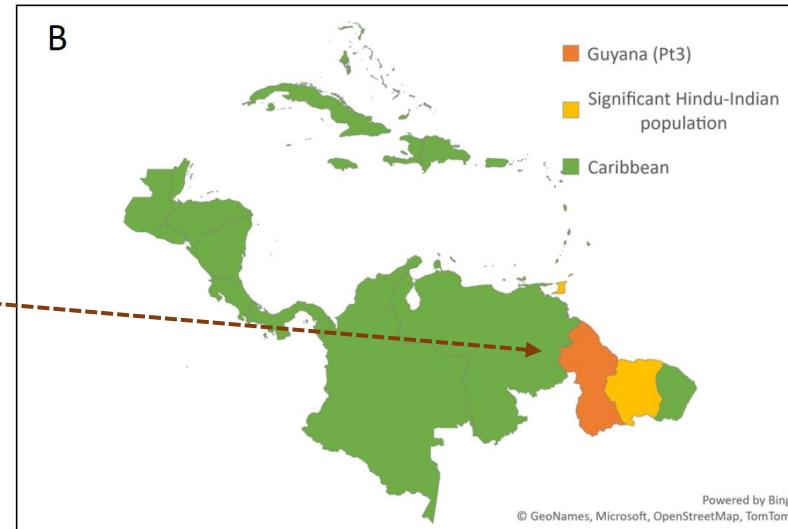
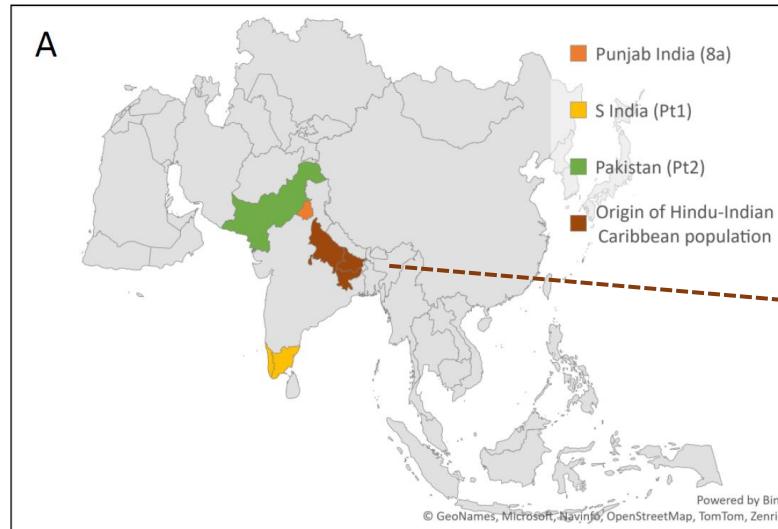
Genotype

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8



# Origins and treatment outcomes of the novel variants

Patient (gender)	Country of birth	Ethnicity	Initial GT (assay)	HCV-GLUE	Geno2pheno[hcv]			Homology	DAA regimen	Treatment outcome
					NS3	NS5a	NS5b			
Pt1 (M)	India (Kerala)	Asian	5a (LiPA)	HCV (unknown subtype)	6w (74.2%)	5a (70.8%)	6xa (73.4%)	8a (74.5%)	SOF/VEL (12 weeks)	SVR12
Pt2 (F)	Pakistan	Asian	Untyped (NS5b sequencing)	HCV (unknown subtype)	6xb (71.1%)	4d (69.7%)	4q (73.0%)	8a (81.5%)	SOF/VEL (5 weeks*)	SVR12
Pt3 (F)	Guyana	Indo-Asian	1 – unspecified subtype (NS5b sequencing)	HCV (unknown subtype)	6r (75.3%)	6*12 (72.4%)	6a (76.5%)	6j (71.2%)	GP (8 weeks)	SVR12



- 1838-1917 (230,000 indentured labourers)

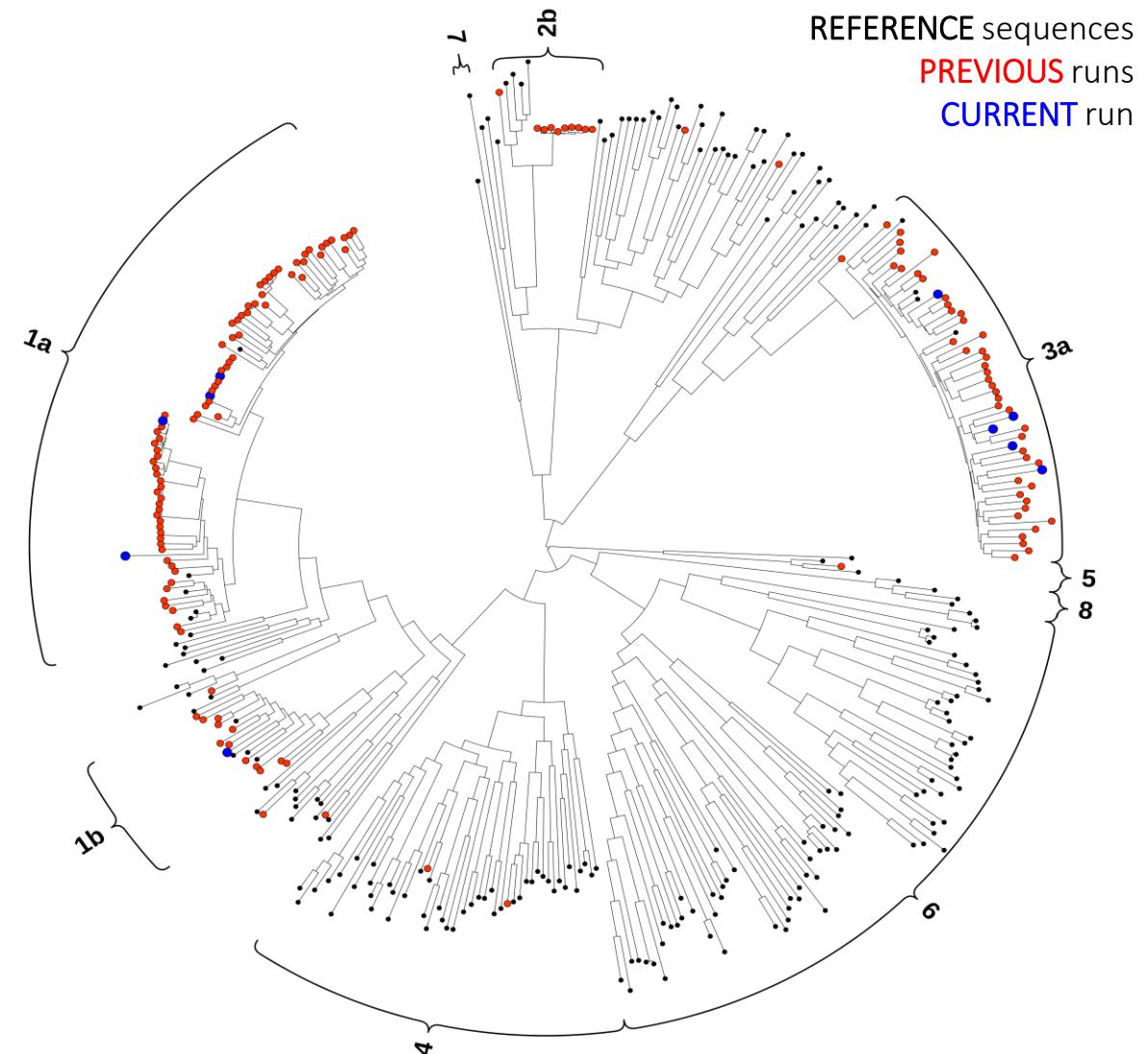
# **Tracking of HCV transmissions and outbreaks**

David Bibby, Sarah Arnold & Laura Phillips

# HCV WGS pipeline quality assurance

## Phylogenetic reconstruction

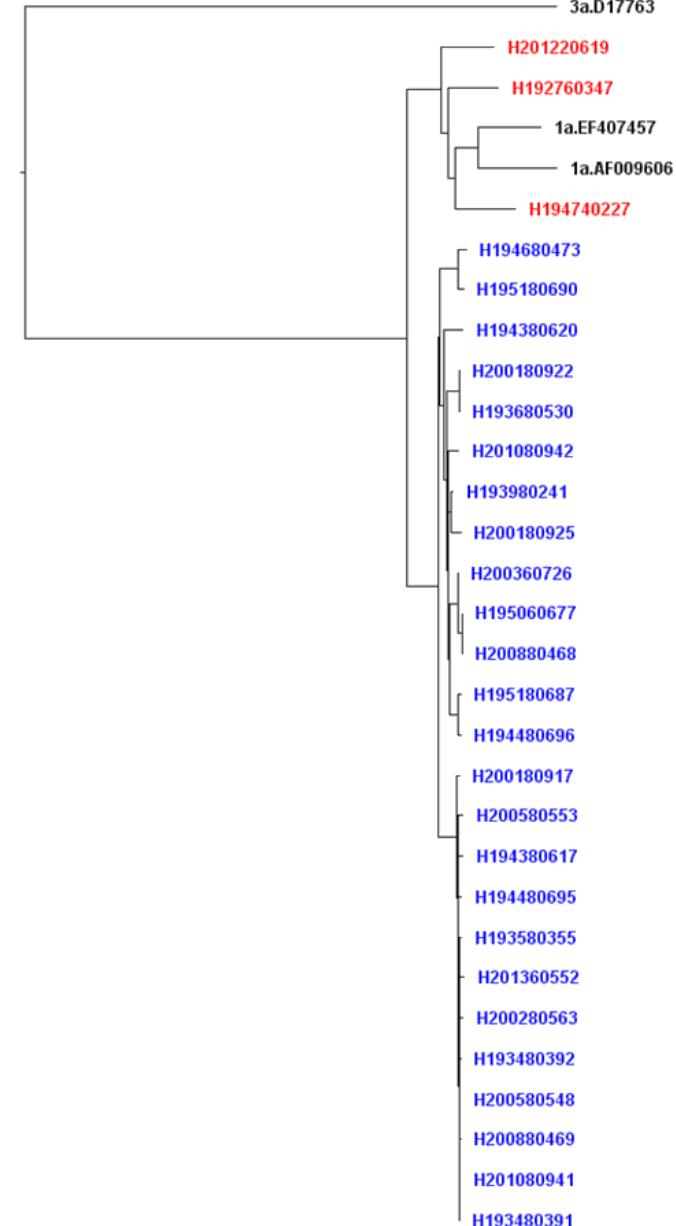
- Generated as routine Quality Control
- Current run plus preceding five runs
- Core, E1, E2, NS3, NS4B, NS5A, NS5B genes
- Closely-related samples:
  - Same patient ?
  - Epidemiological link ?
  - Contamination ?



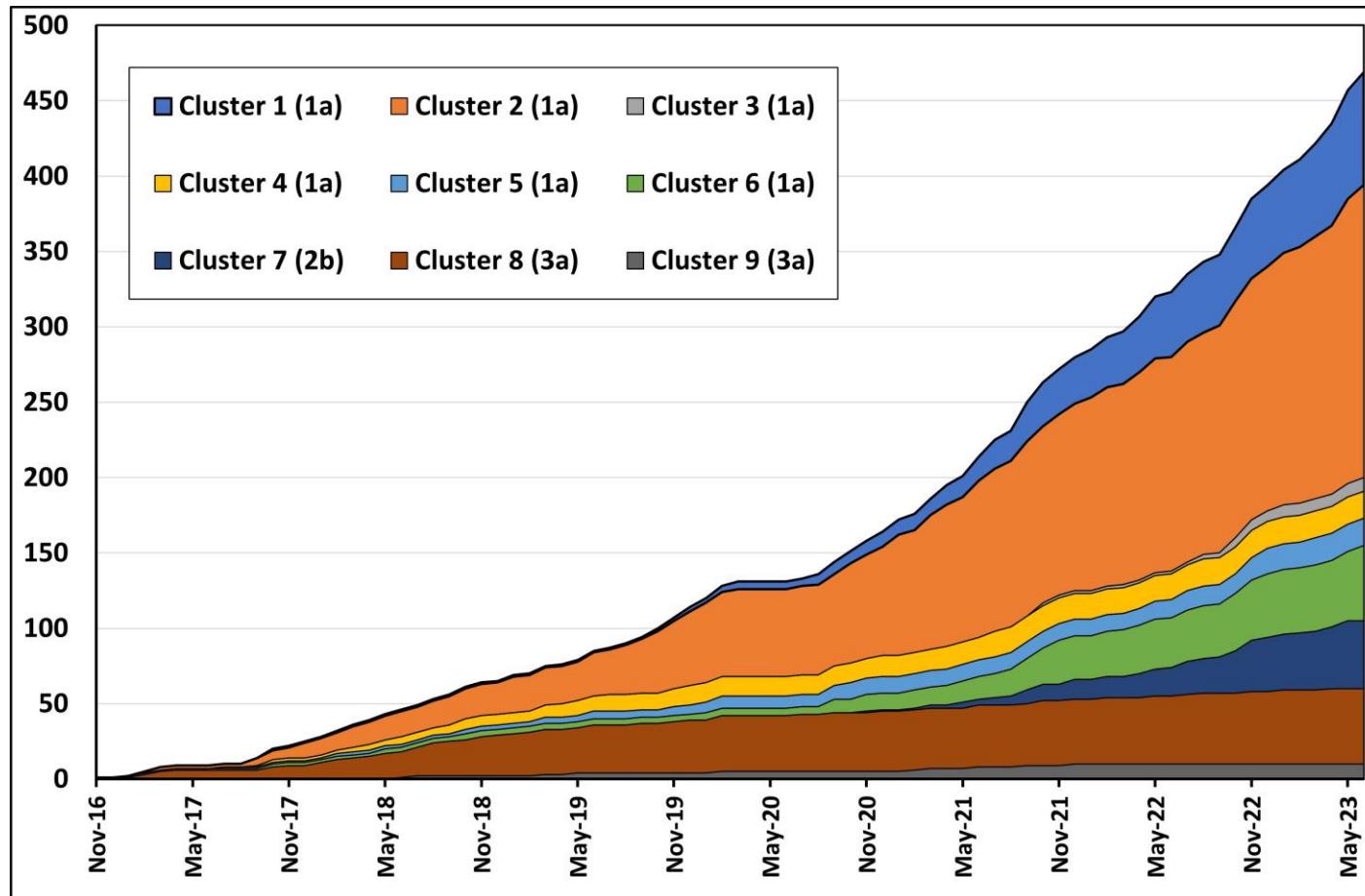
Example of a HCV phylogenetic tree generated for Quality Control purposes

# Serendipitous detection of a cluster in 2020

- Multiple instances of small clusters on QC trees
  - Trees from preceding 6 months of testing were interrogated
  - Large number of linked sequences
- Not contamination
  - All from the same Requestor (“ROYA03” → Northern Ireland)
- Public Health Agency of Northern Ireland (PHA NI) notified
  - Quarterly updates initiated



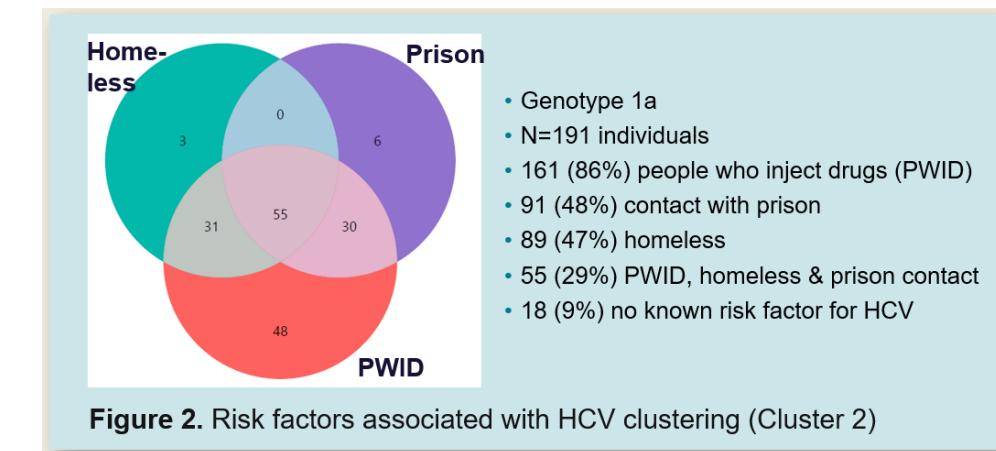
# Northern Ireland HCV transmission clusters



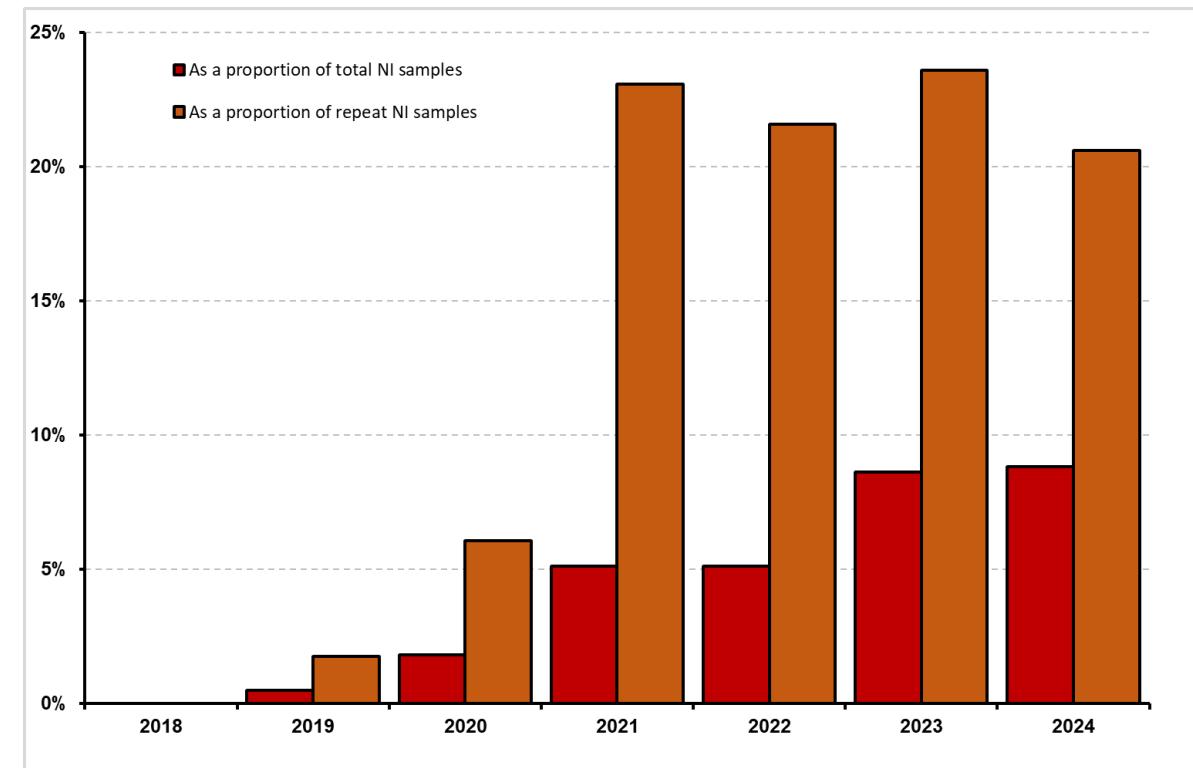
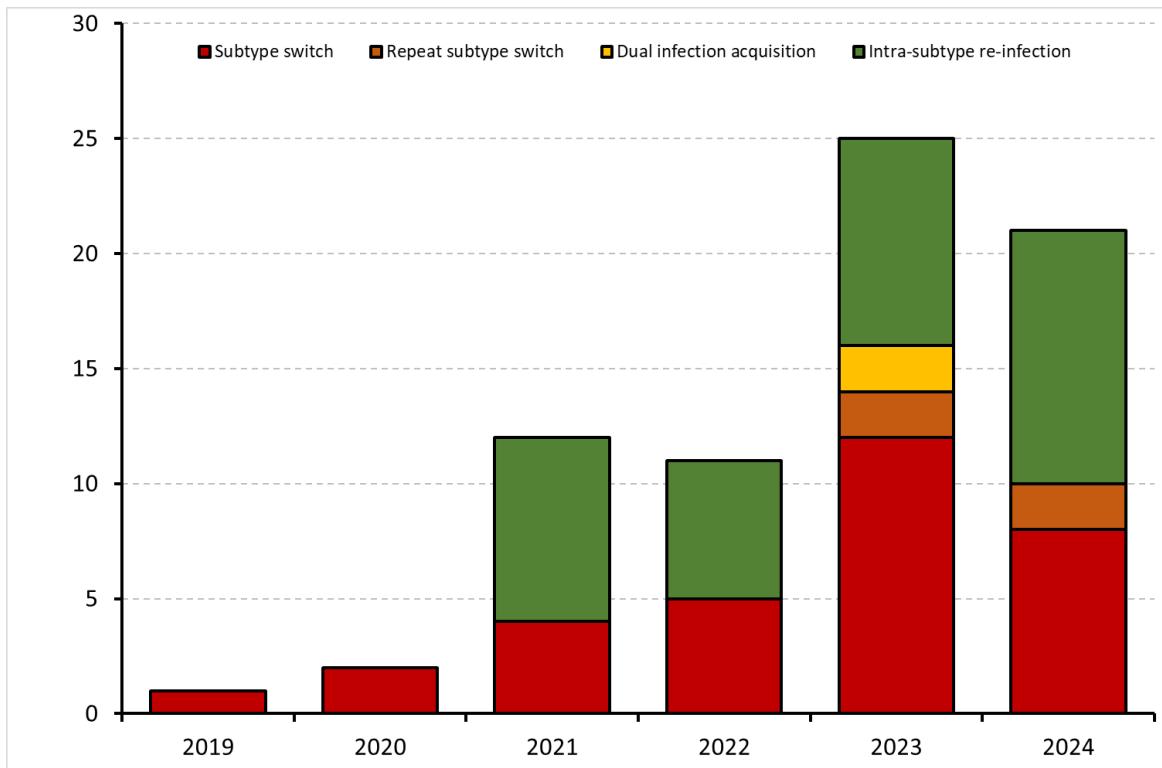
Details of the nine Northern Ireland (NI) HCV clusters

Subtype	Cluster No.	No. individuals	Non-NI	Year*
1a	1	75		2017
	2	191	1	2016
	3	9		2017
	4	18		2017
	5	18		2016
	6	50	1	2020
2b	7	45		2017
3a	8	50		2017
	9	10		2018

\*year of the earliest sample date for the cluster

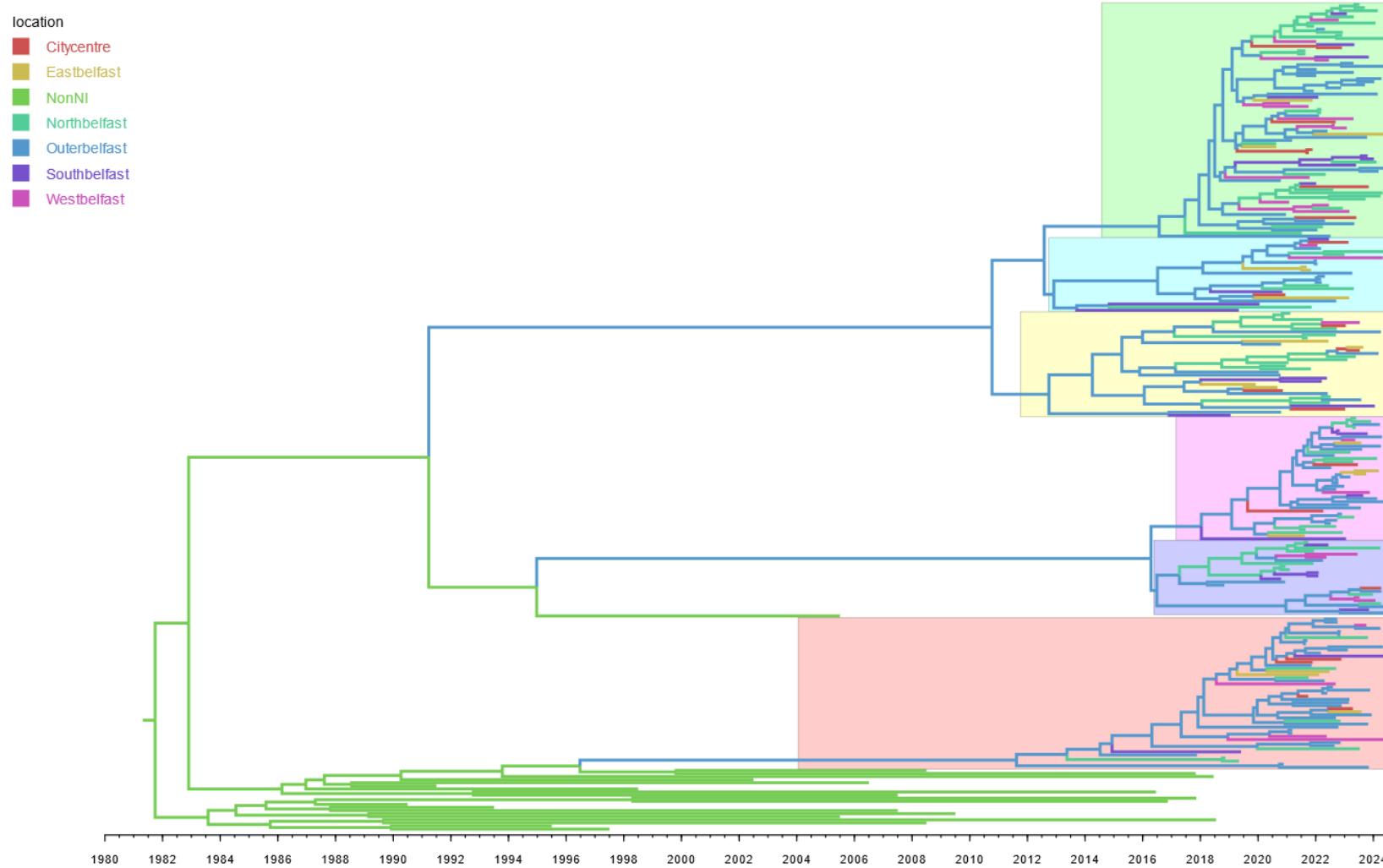


# NI Reinfections



- Genomics is best method for identifying reinfections
- Reinfection is a signal for high-risk behaviour
- It increases pressure on public health resources (prevention & treatment)

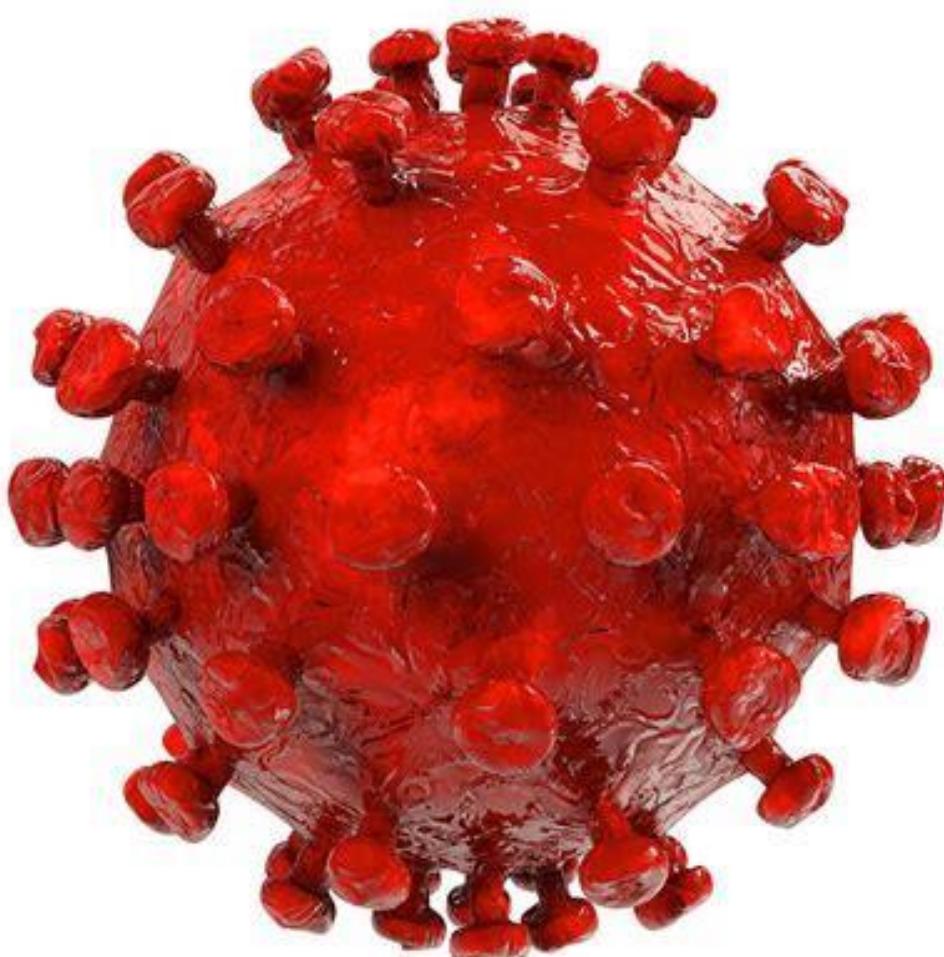
# Phylogeography of Gt1a NI clusters



**Postulated contributory factors to outbreak are mostly related to the COVID-19 pandemic:**

- Reduced support to vulnerable groups with pausing of face-to-face support services
- Pause in BBV screening
- Use of non-standard accommodation
- Movement of people to different areas for accommodation
- Closure of two NSEs in Belfast
- Reported interruption of heroin supply
- Change in injecting habits with more people injecting cocaine and using neck and groin sites

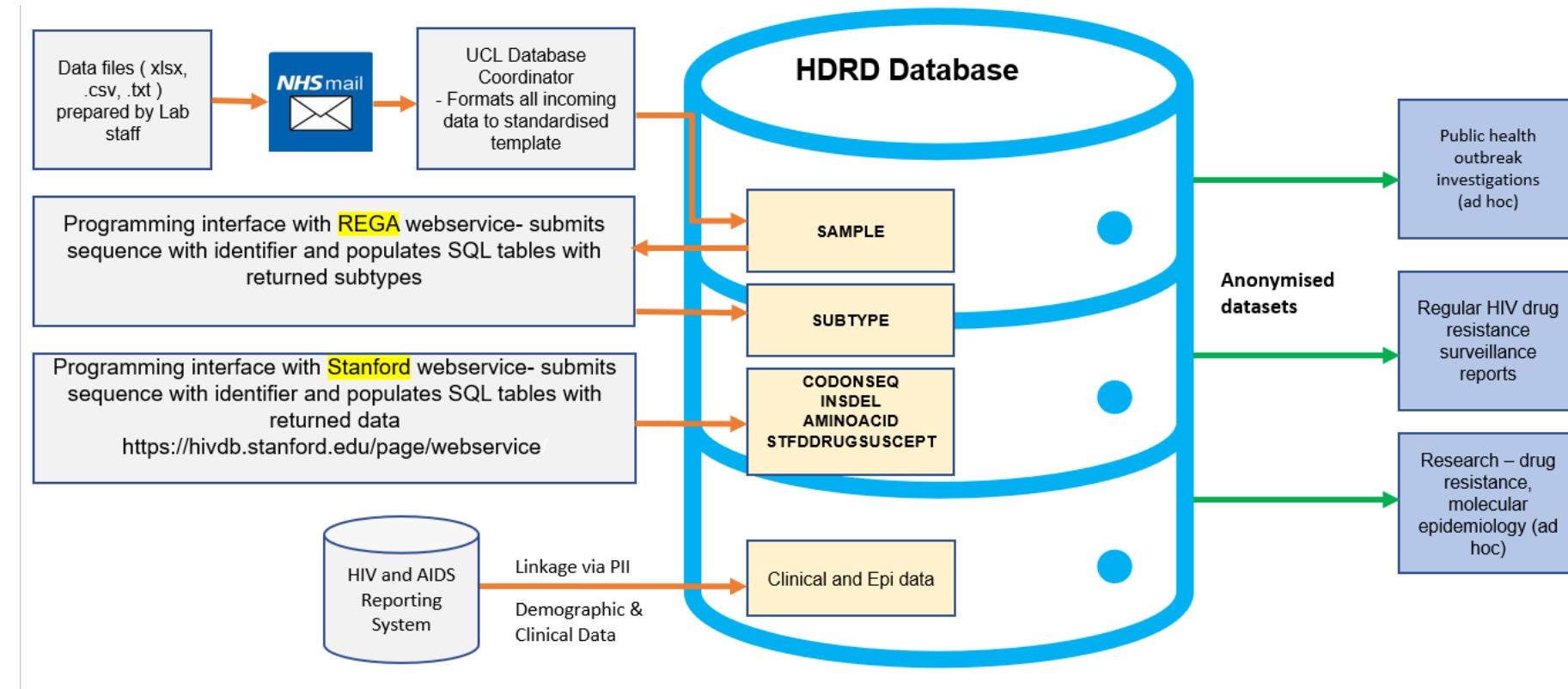
# Human Immunodeficiency Virus (HIV)



## HIV Genomics surveillance programme

- UK HIV Drug Resistance Database to UKHSA
- Antiviral resistance surveillance

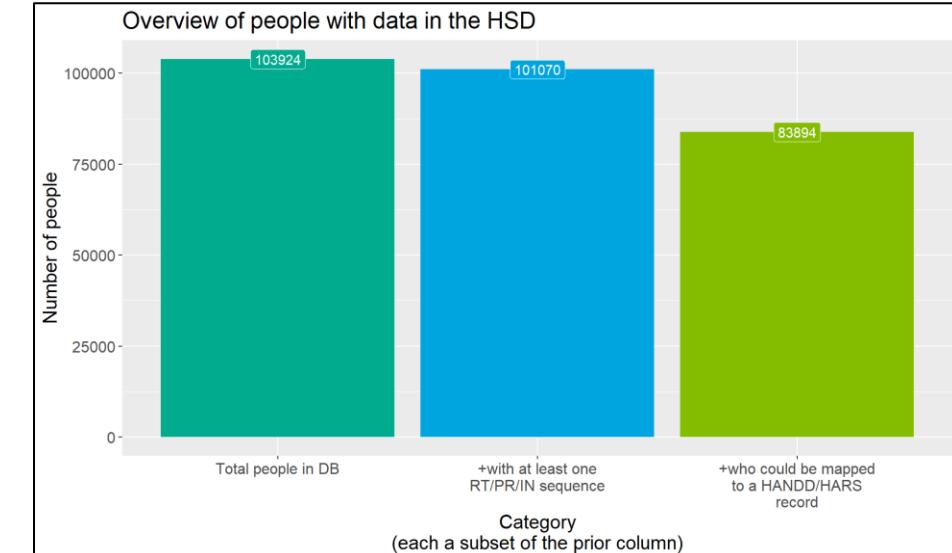
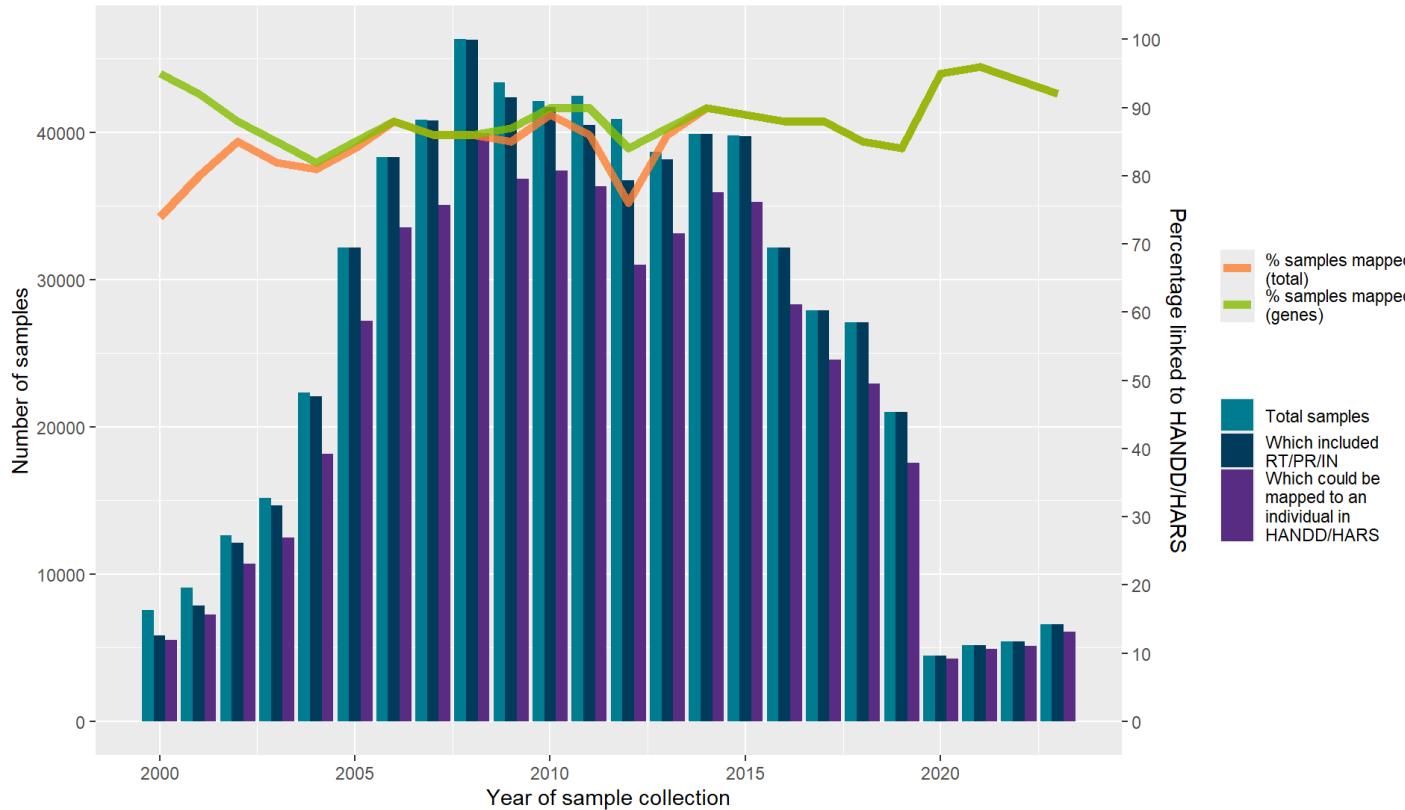
# UK HIV Drug Resistance Database (UK-HDRD)



- Central repository of HIV sequence data in the UK generated as part of routine clinical care since 2001
- Funded by MRC as a research study and hosted at UCL until 2019
- Transferred to UKHSA in 2024 to be used for public health surveillance

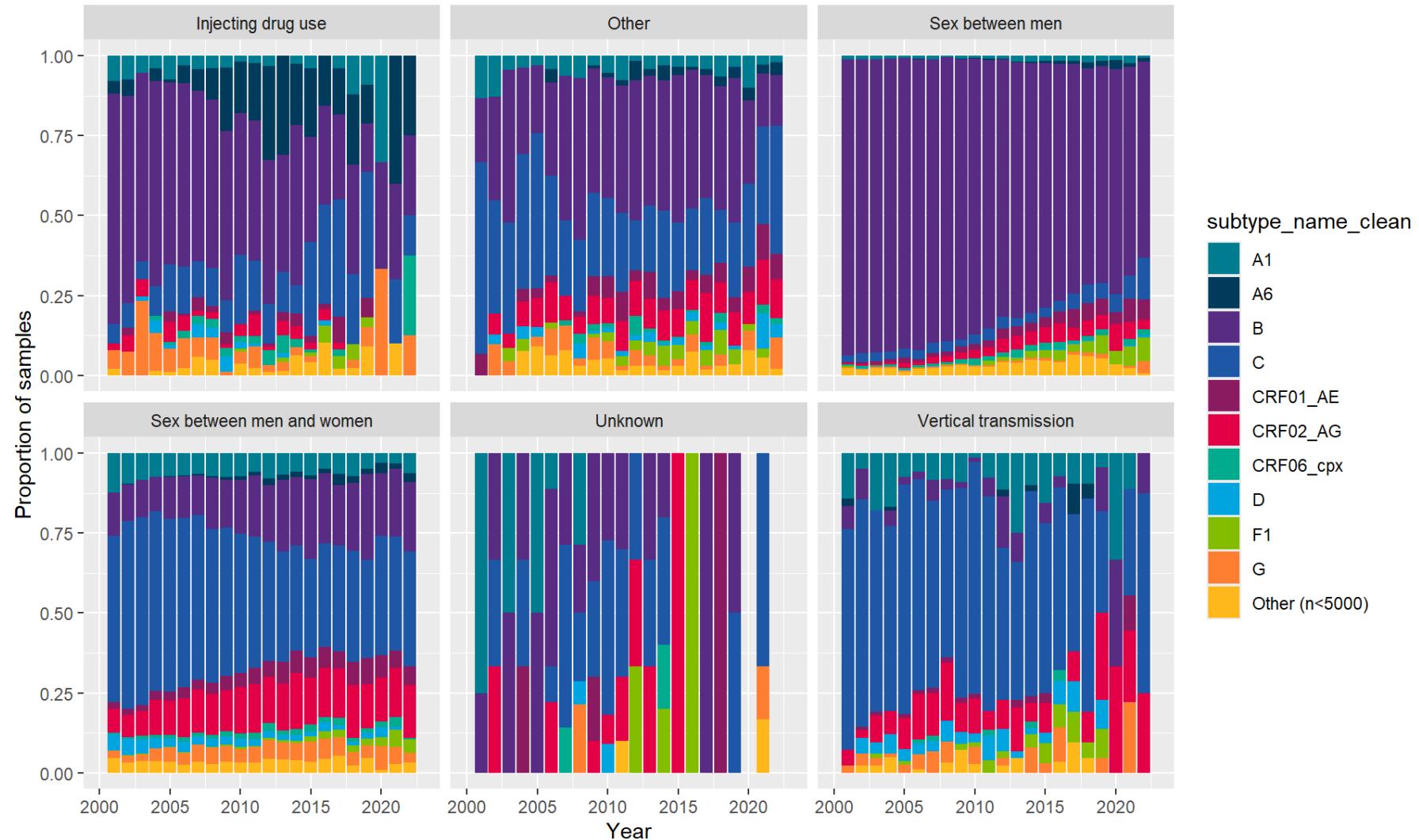
# Current data held in UK HIV Genomics Database

Overview of sample count and linkage, by year

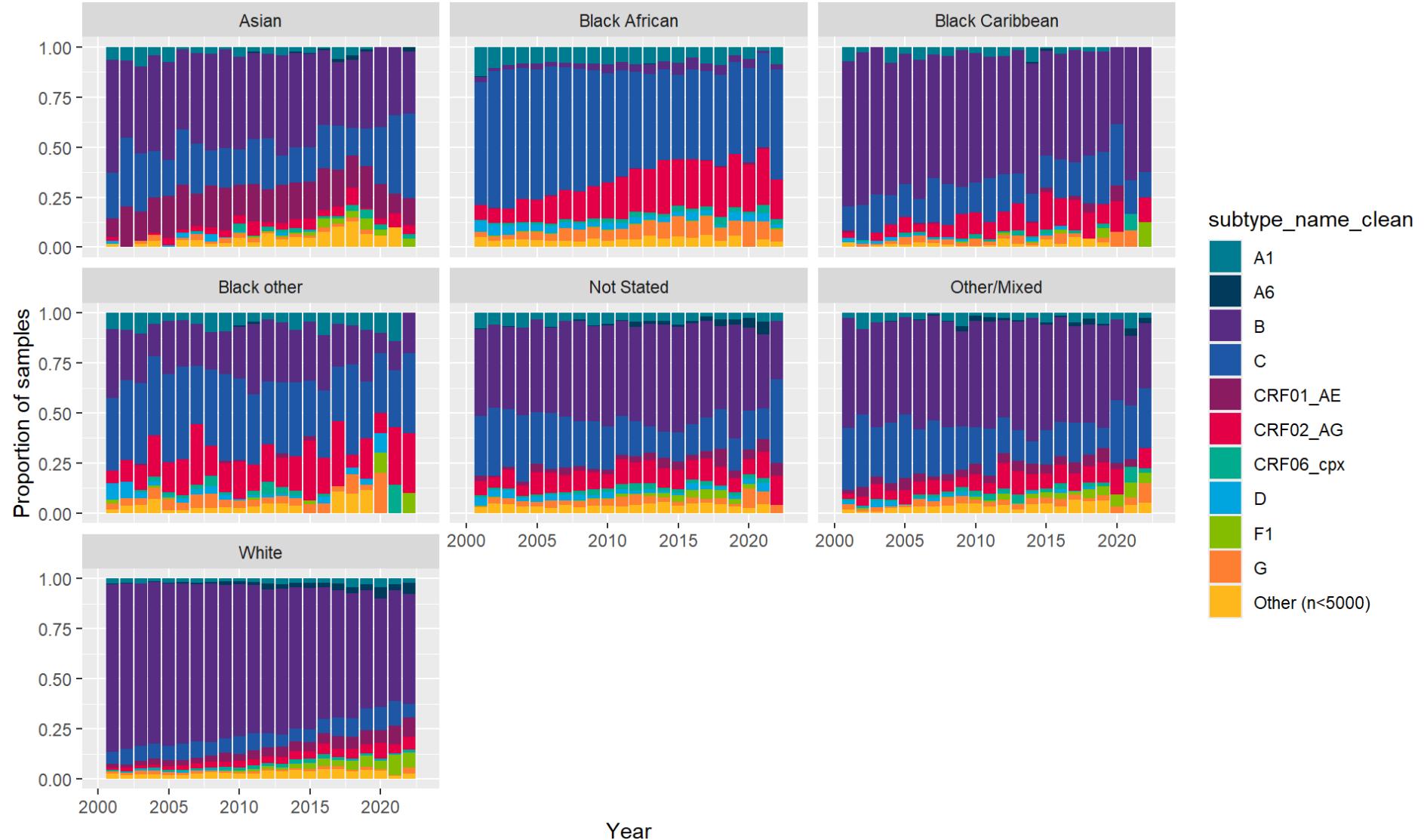


- Data up to 2019 transferred from UCL
- Post-2019 data being collected directly from NHS and PH labs
- High proportion of sequences linked to epidemiological and clinical data

# Subtype distribution by risk population



# Subtype distribution by ethnicity



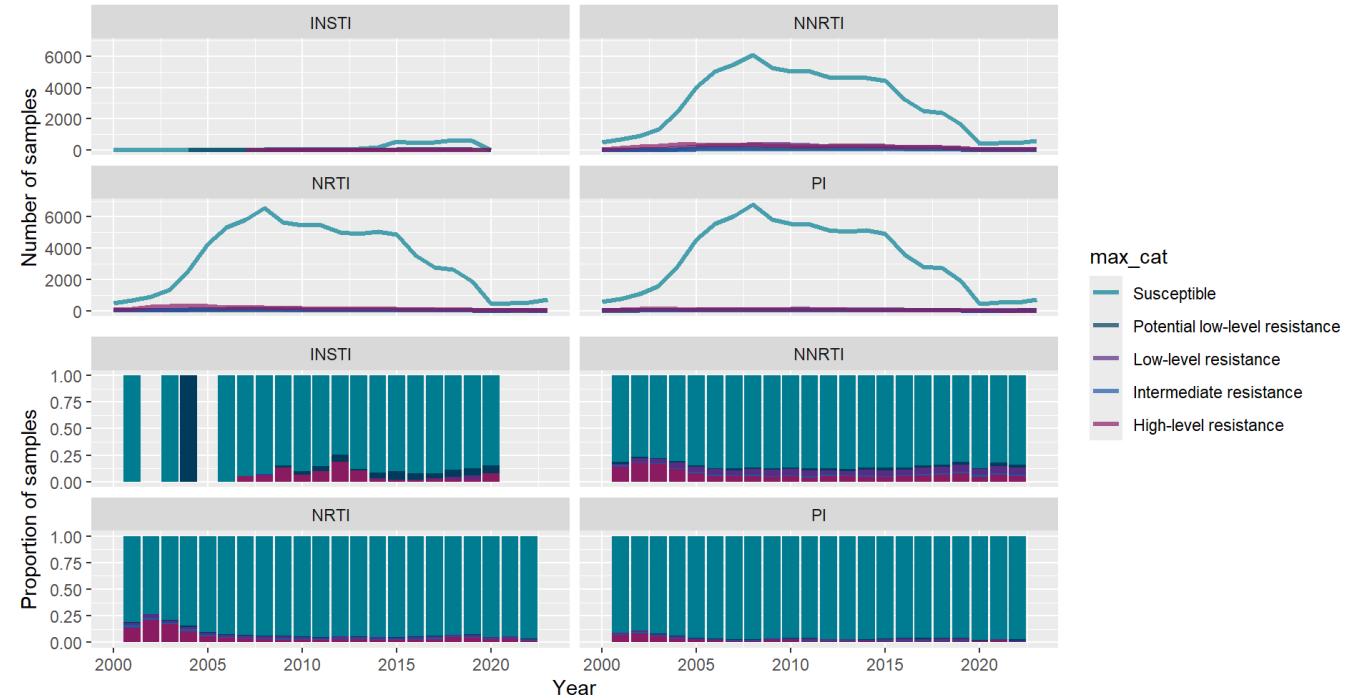
# Prevalence of drug resistance

Summary of drug class resistance by collected\_year,  
First result only?: FALSE  
Treatment status?: treated



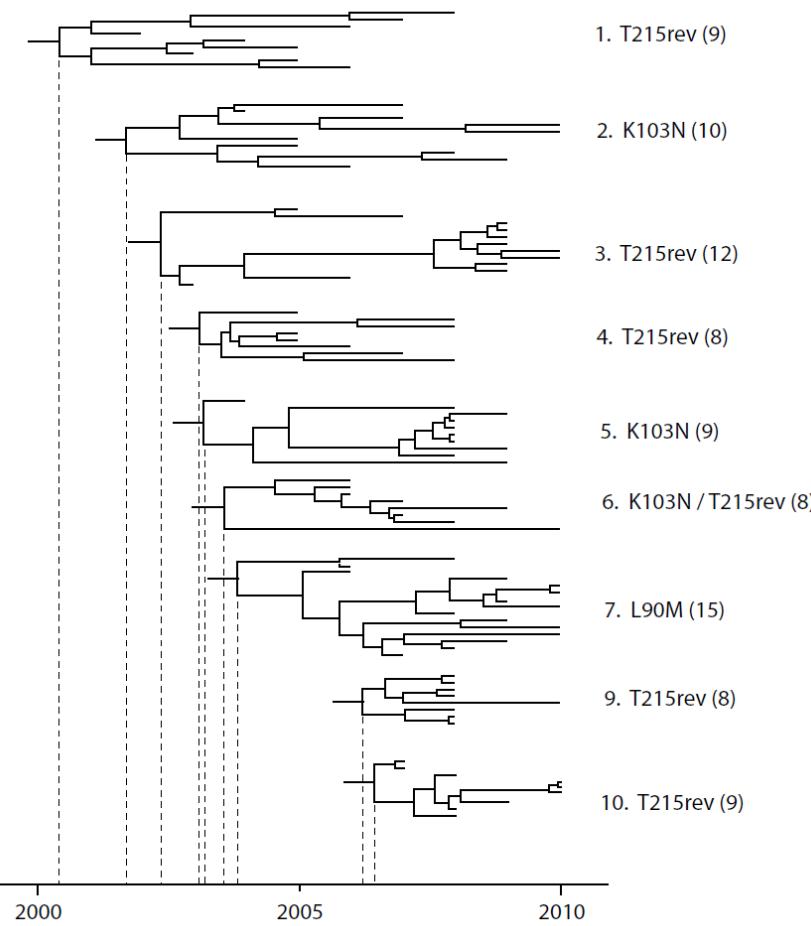
Treatment-experienced

Summary of drug class resistance by collected\_year,  
First result only?: FALSE  
Treatment status?: untreated



Treatment-naïve

# Prevalence of HIV-1 transmitted drug resistance



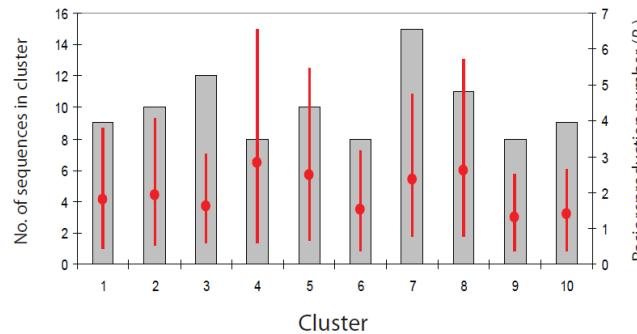
## Evidence of Self-Sustaining Drug Resistant HIV-1 Lineages Among Untreated Patients in the United Kingdom

Jean L. Mbisa,<sup>1</sup> Esther Fearnhill,<sup>2</sup> David T. Dunn,<sup>2</sup> Deenan Pillay,<sup>3</sup> David Asboe,<sup>4</sup> and Patricia A. Cane<sup>1</sup>; for the UK HIV Drug Resistance Database

<sup>1</sup>Antiviral Unit, Virus Reference Department, Public Health England, <sup>2</sup>Medical Research Council Clinical Trials Unit, and <sup>3</sup>Research Department of Infection, University College London, and <sup>4</sup>Chelsea and Westminster Hospital, London, United Kingdom

(See the Editorial Commentary by Kouyos and Günthard on pages 837–9.)

- Discordance between mutations patterns in treatment failure and TDR
- Large clusters of most common TDR mutations up to 8 years old
- Basic reproductive number ( $R_0$ ) of the large clusters  $>1$



# InSTI resistance surveillance: INITIO study

- Modelling shows that if headline TDR is 1-5% it is cost effective to perform baseline resistance testing
- No requirement for baseline integrase resistance testing as resistance is  $\leq 1\%$
- Treatment failures mostly with low-level vireamia for those on InSTI-based therapies
- ~50% have no resistance mutations in integrase gene
- ?Role of mutations outside integrase gene

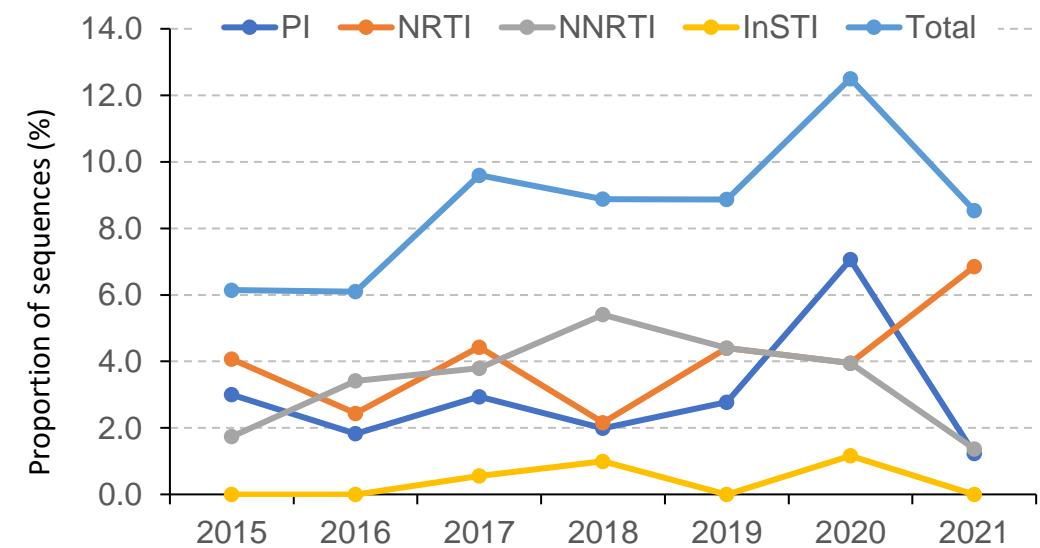
*J Antimicrob Chemother* 2020; **75**: 3311-3318  
doi:10.1093/jac/dkaa309 Advance Access publication 29 July 2020

Journal of  
Antimicrobial  
Chemotherapy

## Surveillance of HIV-1 transmitted integrase strand transfer inhibitor resistance in the UK

Jean L. Mbisa  <sup>1,2\*</sup>†, Juan Ledesma <sup>1,2†</sup>, Peter Kirwan <sup>1</sup>, David F. Bibby <sup>1</sup>, Carmen Manso <sup>1</sup>, Andrew Skingsley <sup>1</sup>, Gary Murphy <sup>1</sup>, Alison Brown <sup>1</sup>, David T. Dunn <sup>3</sup>, Valerie Delpech <sup>1,2</sup> and Anna Maria Geretti <sup>4</sup>

<sup>1</sup>National Infection Service, Public Health England, London, UK; <sup>2</sup>National Institute for Health Research (NIHR) Health Protection Research Unit in Blood Borne and Sexually Transmitted Infections, London, UK; <sup>3</sup>Institute for Global Health, University College London, London, UK; <sup>4</sup>Institute of Infection and Global Health, University of Liverpool, Liverpool, UK





# **The future of HIV and HCV genomics programmes for public health surveillance in the UK**

# HCV and HIV elimination goals

- In 2016, WHO set goals to eliminate viral hepatitis as a major public health threat by 2030
  - 80% reduction in incidence ( $\leq 5$  new annual HCV infections/100 000 persons)
  - 65% reduction in mortality rates (absolute HCV-related mortality rate of  $\leq 2/100 000$  per year)  
[compared to 2015 baseline]
- In 2021, UK Government published “*Towards Zero: the HIV Action Plan for England 2022-2025*”

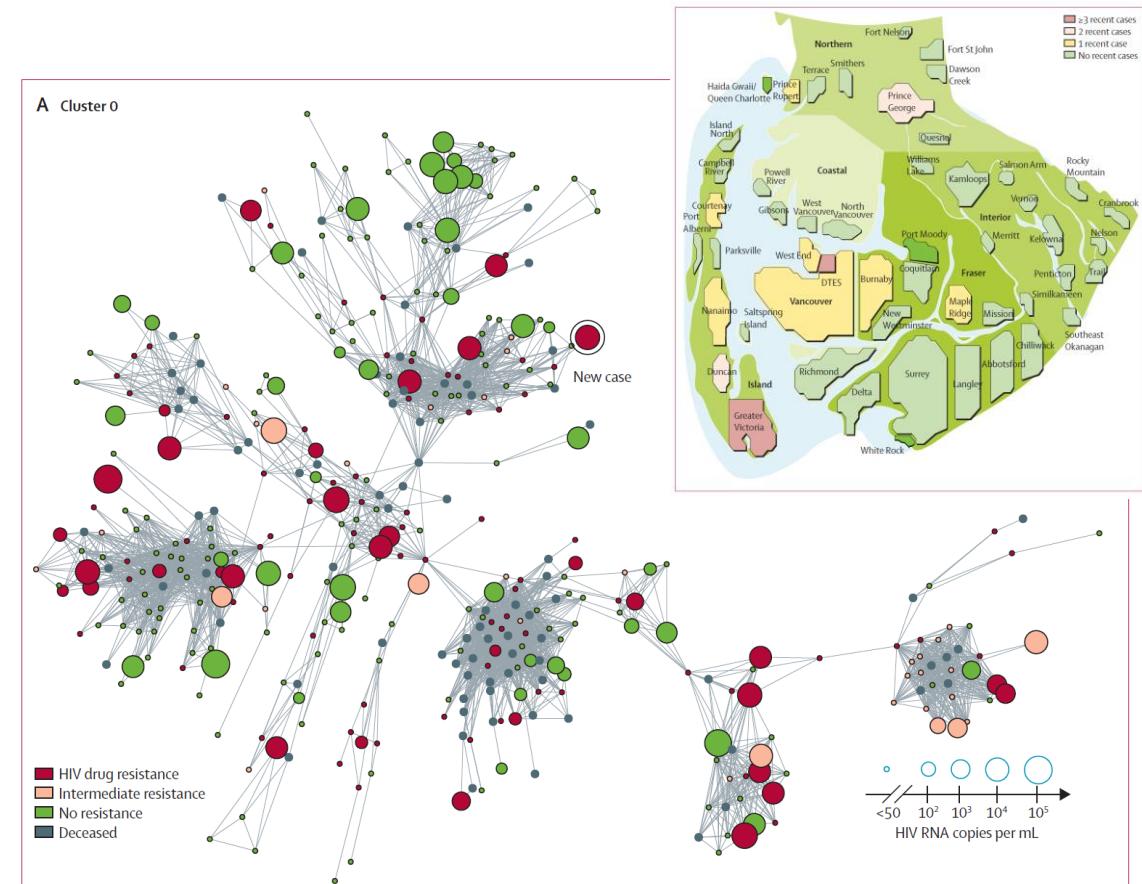
**Genomic surveillance has a role to play and the closer we come to the end game the more important it will become**

# Cluster detection and response (CDR)

- PH, HCW or community members who notice changes in patterns of new diagnoses
- Analyses of surveillance data during a specific period in a particular geographic region
- **Analyses of HIV molecular data to identify clusters of closely related sequences indicating rapid transmission**

Near real-time monitoring of HIV transmission hotspots from routine HIV genotyping: an implementation case study

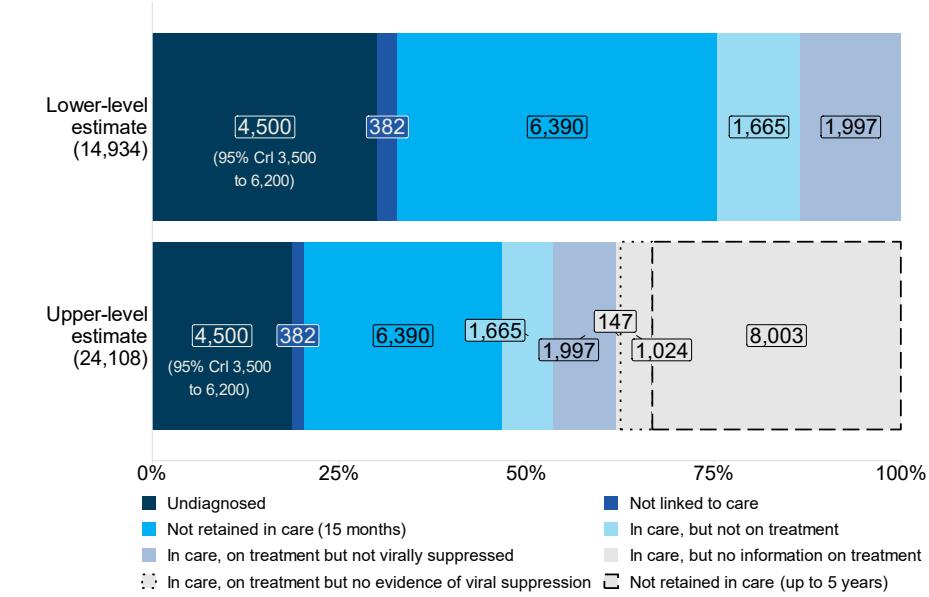
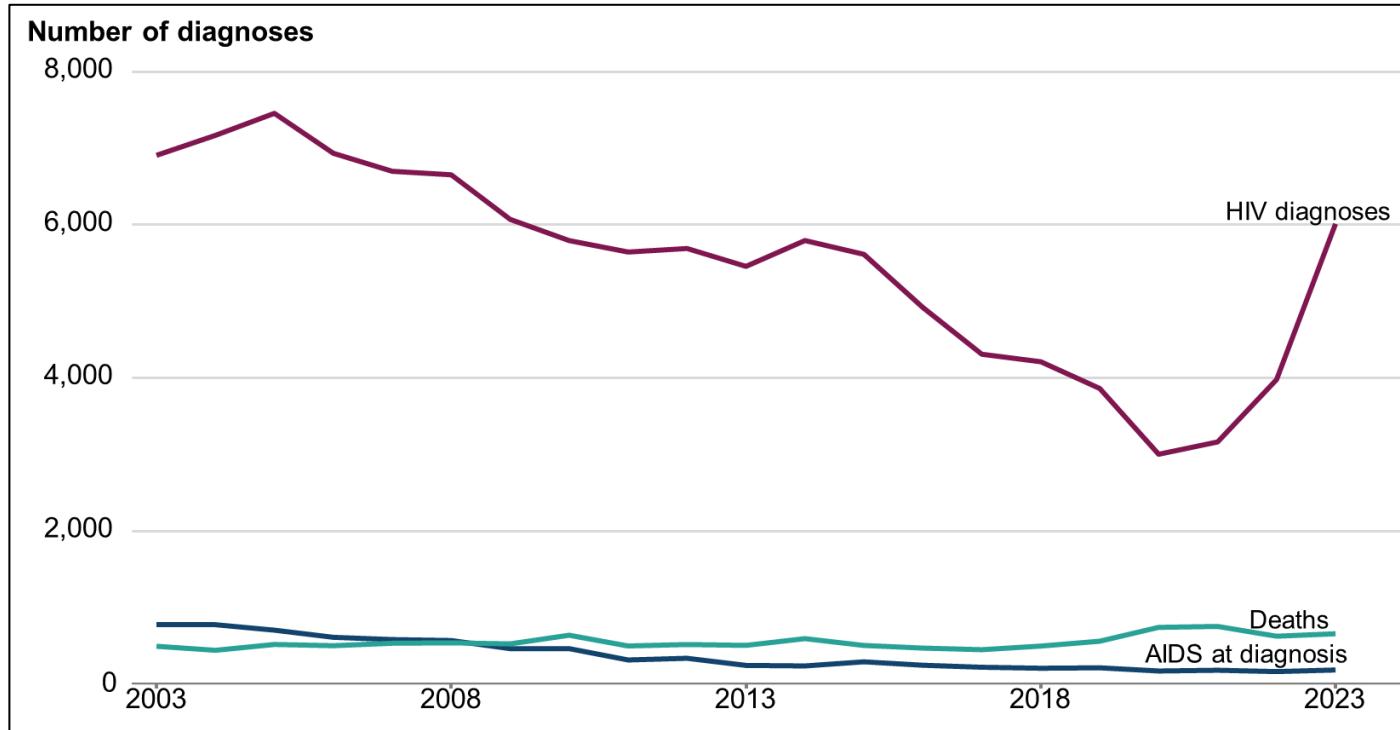
Art FY Poon, Réka Gustafson, Patricia Daly, Laura Zerr, S Ellen Demlow, Jason Wong, Conan K Woods, Robert S Hogg, Mel Krajden, David Moore, Perry Kendall, Julio S G Montaner, P Richard Harrigan



# Unanswered questions on CDR

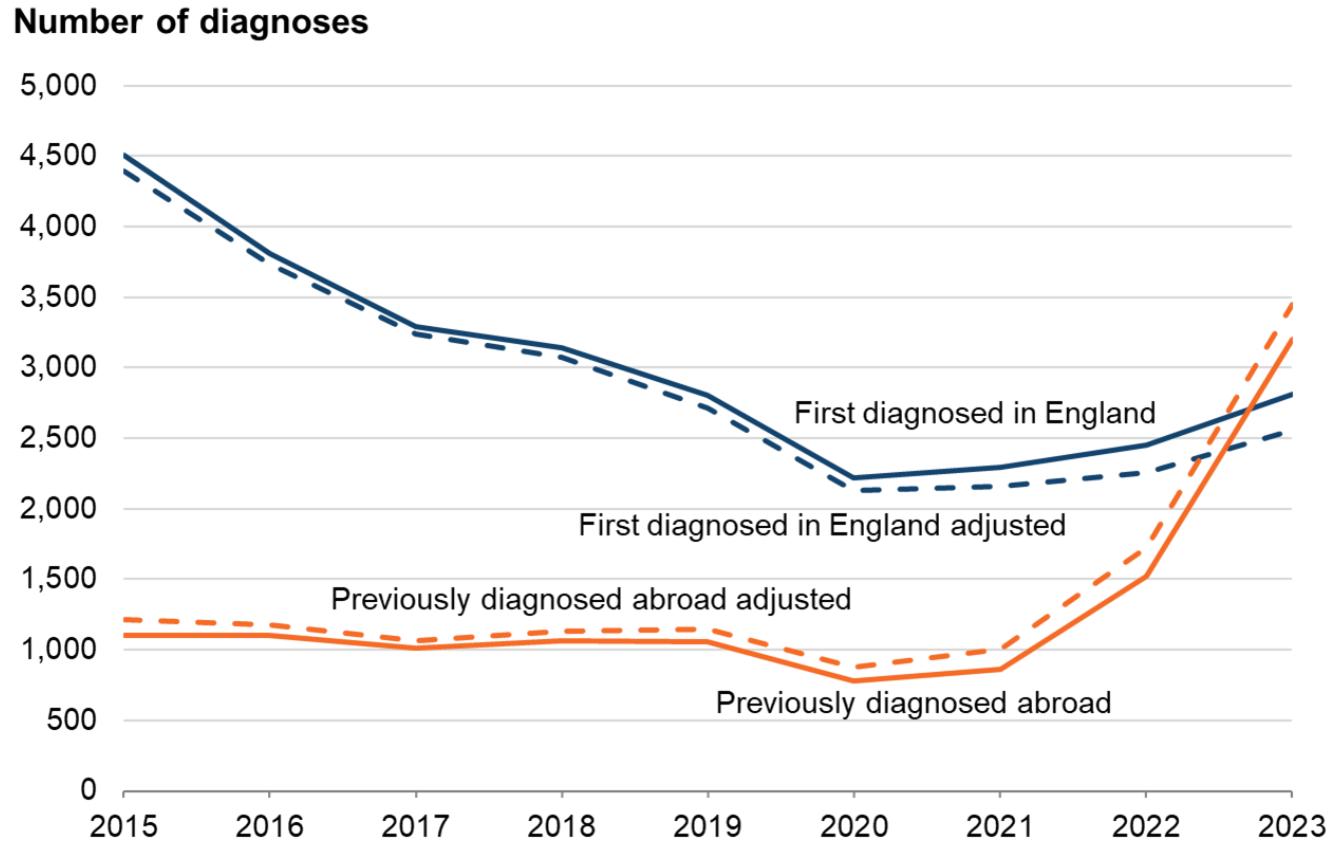
- **Phylogenetic and data analytical tools**
  - More frequent and automated data ingestion
  - Definition of an epidemiologically significant cluster (thresholds, size, growth rate, risk factors, phylogenotypes)
  - Tools that can scale
- **Public health added value**
  - Current evidence is anecdotal and theoretical and mostly from PWID risk population
  - Needed for policymaking and funding of CDR programmes
- **Ethics**
  - Sequence data linked to metadata can be very identifying and source attribution is possible
  - Safeguards to reassure data providers that it won't be used by non-health providers and other parts of the government (CPS, HO)
  - Engagement of key stakeholders especially community representatives

# Non-cluster use of genomics data: elimination targets

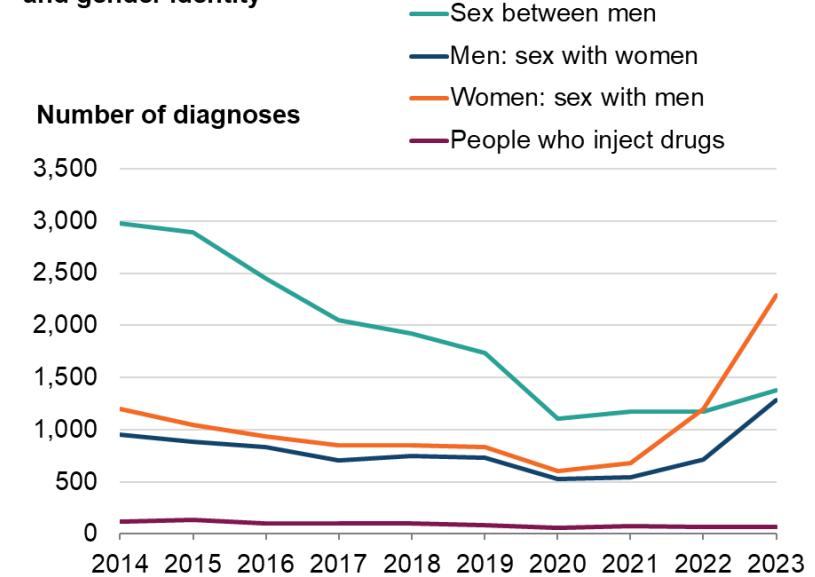


- **Incidence**
  - Not all new diagnoses are incident
  - Need to estimate incidence to understand local transmission rates (currently use CD4 back-calculation and other biomarkers)
  - Migration is a confounder
- **Undiagnosed**
  - Need to estimate undiagnosed population as they are contributors to ongoing transmission

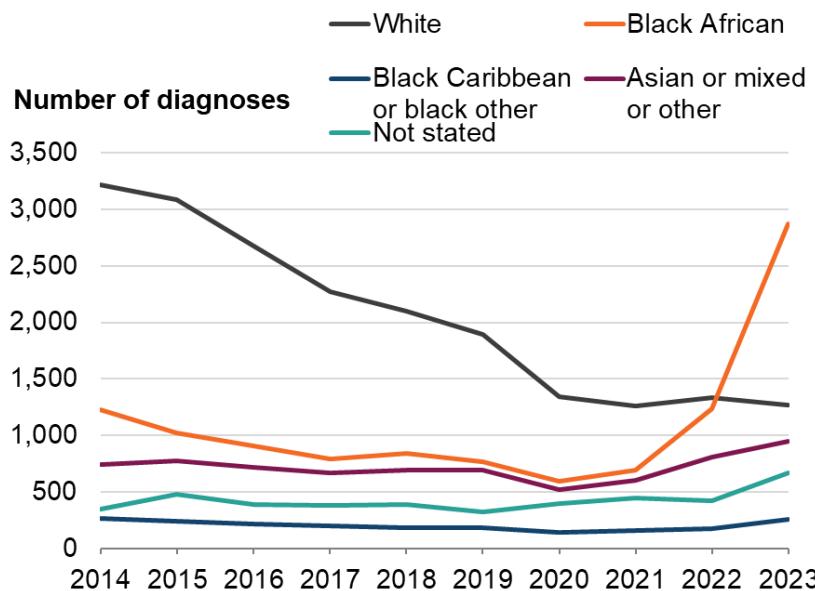
# Impact of migration on HIV data



a) Probable route of exposure and gender identity

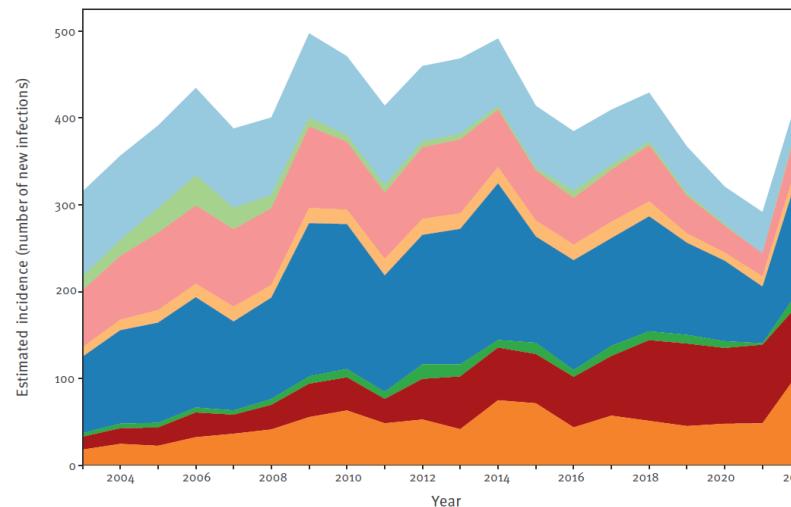


a) Ethnic group

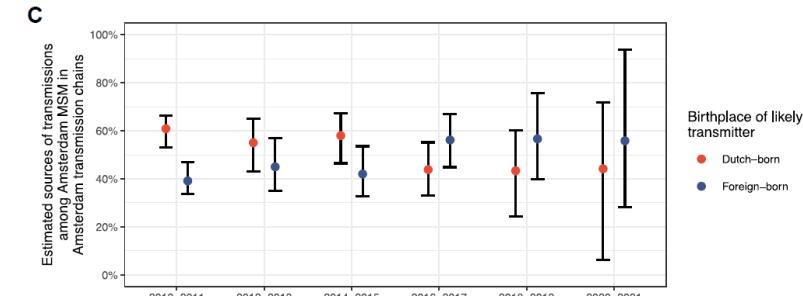
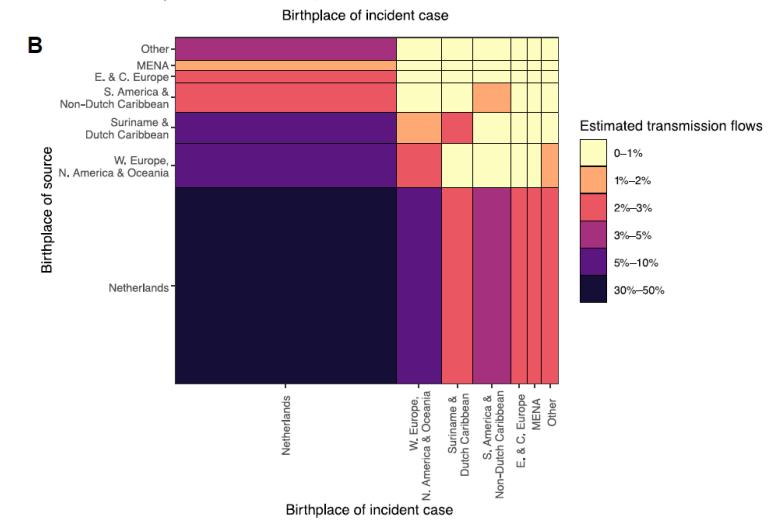
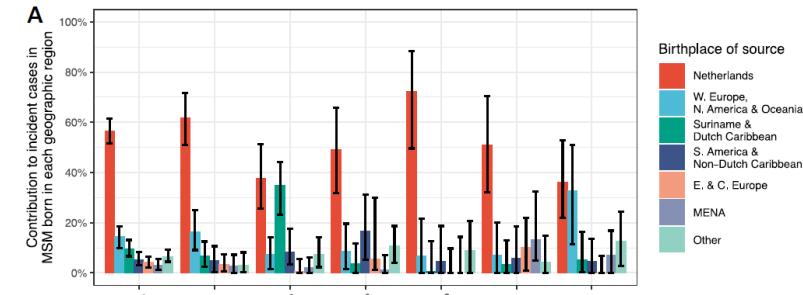
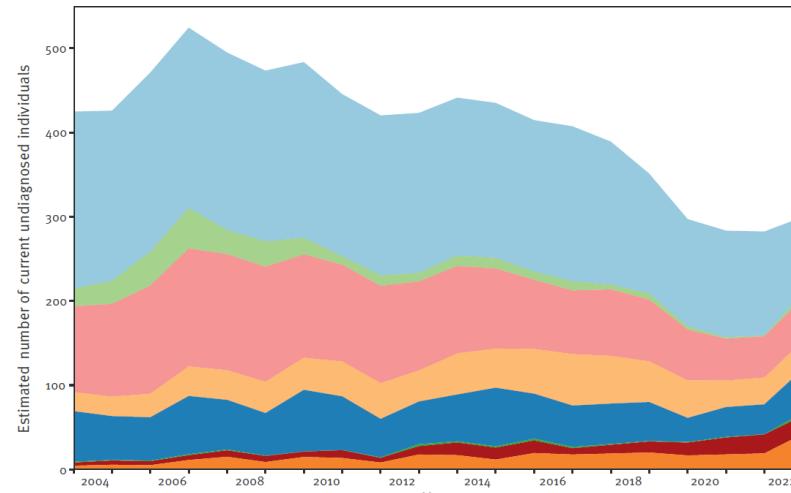


# Incorporating HIV genomics data into estimating incidence & undiagnosed

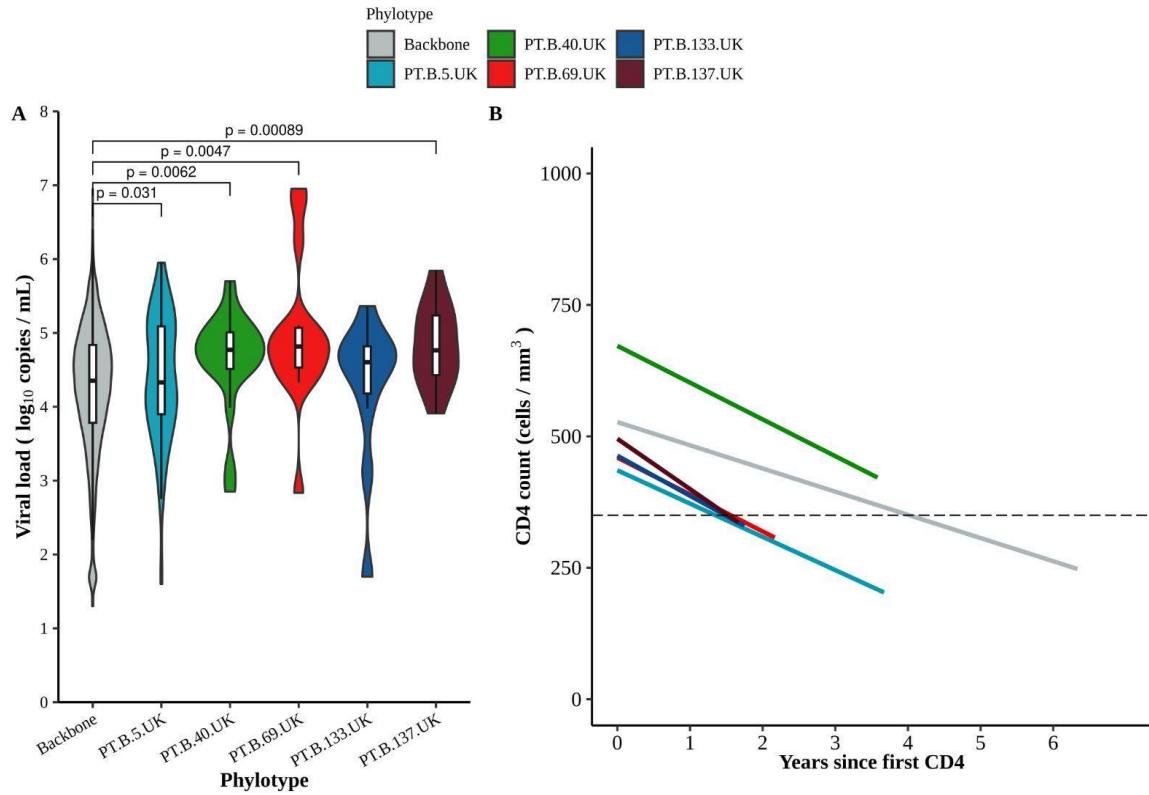
Estimating yearly incidence



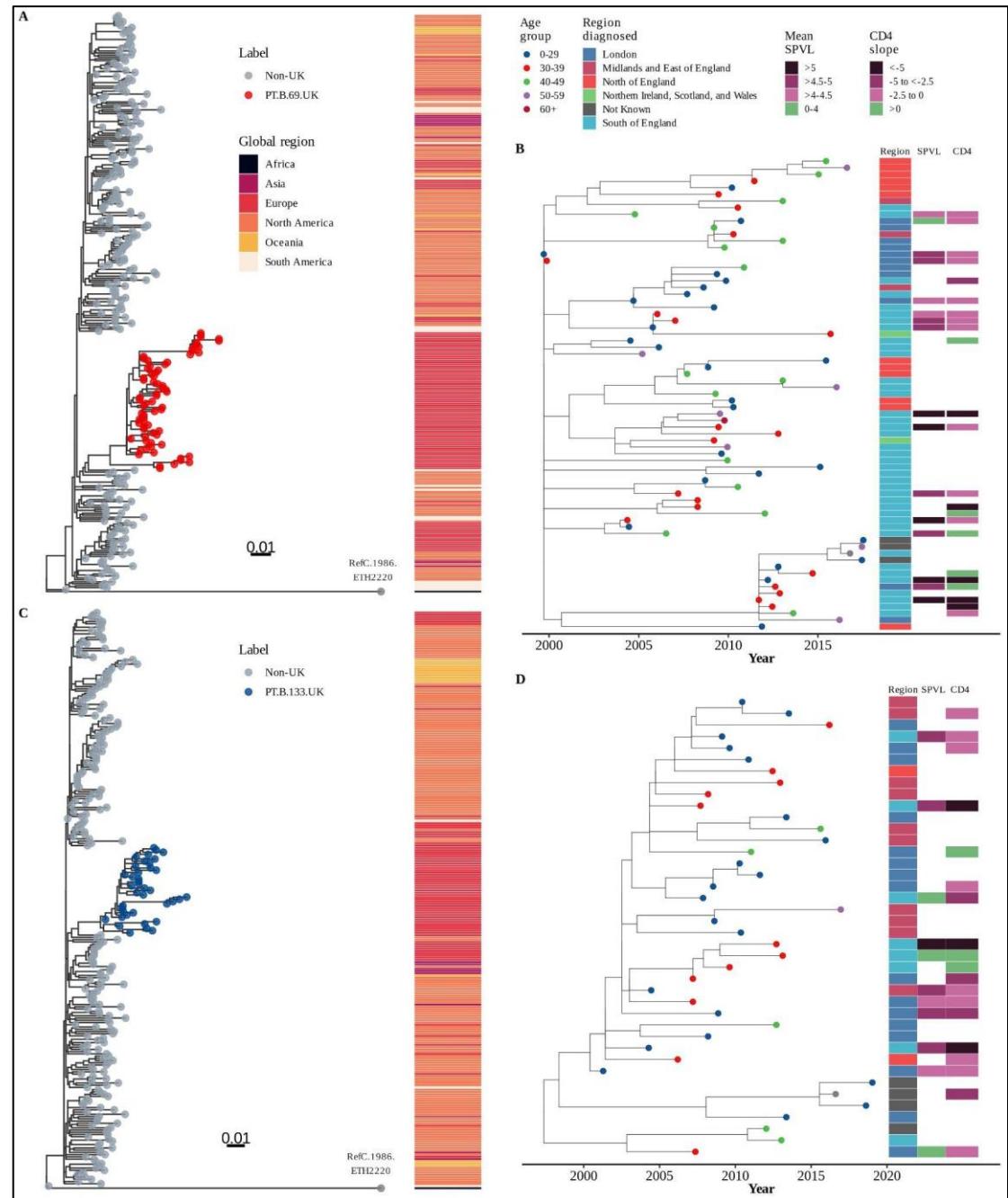
Estimating yearly undiagnosed



# UK HIV phylotypes

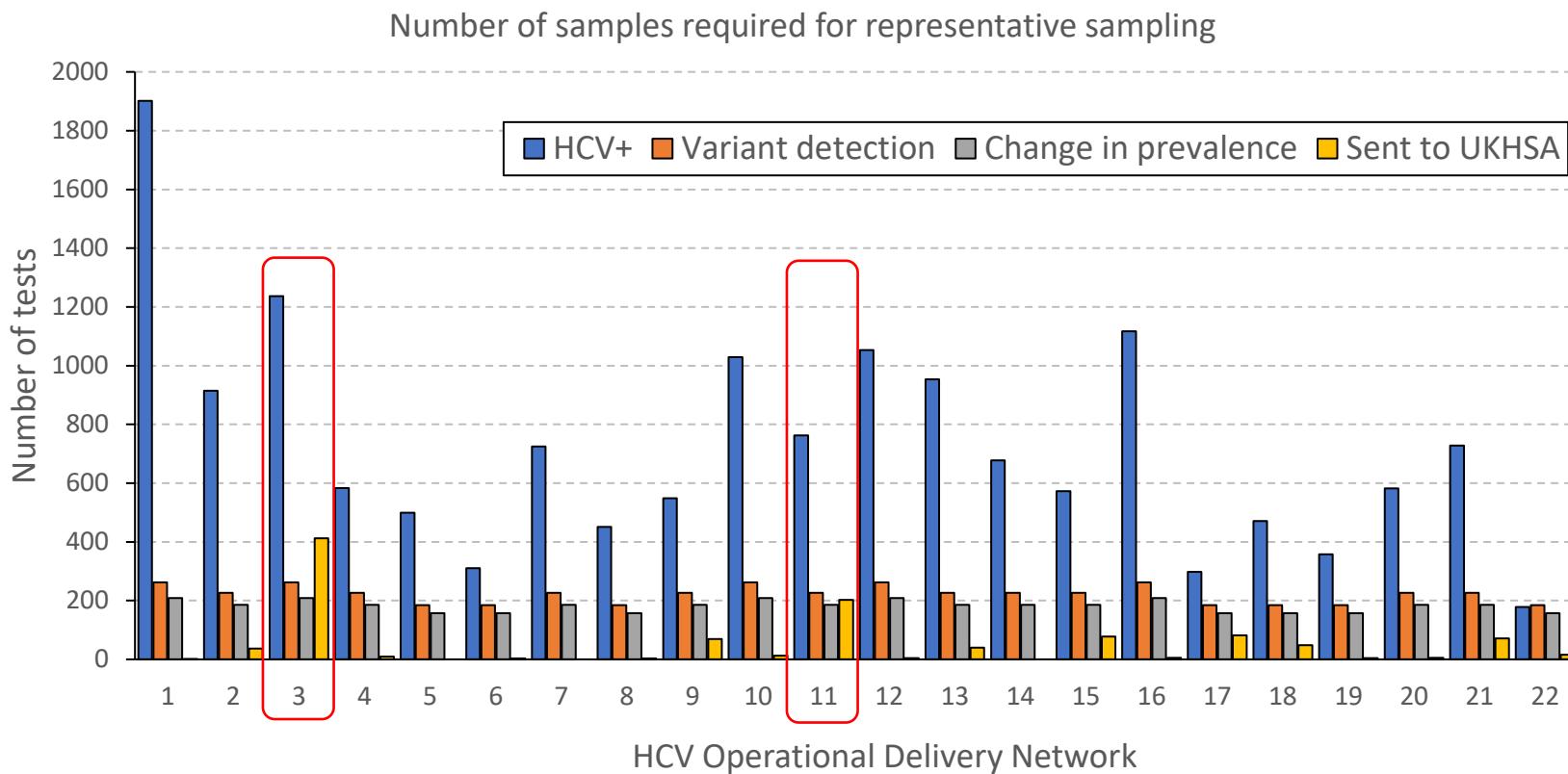


Vinicius Franceschi & Erik Volz



# How about HCV?

- Density of sampling is insufficient from samples processed in the clinical pathway
- HCV Genomics Surveillance Programme launched in November 2024



## Hepatitis C Operational Delivery Networks and clinical leads



Hepatitis C Operational Delivery Networks and clinical leads	
<b>North</b>	<b>London Central North West</b>
1. North East & North Cumbria The Newcastle Upon Tyne Hospitals NHS Foundation Trust Stuart McPherson	21. Bristol and Severn Hep C ODIN University Hospitals Bristol NHS Foundation Trust Fiona Gordon
2. Greater Manchester & East Cheshire Manchester University NHS Foundation Trust Javier Vilar	13. North Central London Viral Hepatitis Network Royal Free London NHS Foundation Trust Douglas MacDonald
3. Cheshire & Merseyside Royal Liverpool & Broad Green University Hospital NHS Trust Paul Richardson, Libuse Ratcliffe	14. Barts Barts Health NHS Trust Graham Foster
4. South Yorkshire Sheffield Teaching Hospitals NHS Foundation Trust Benjamin Stone	15. South Thames Hepatitis Network (STHePNet) Kings College Hospital NHS Foundation Trust Kosh Agarwal
5. Humber and North Yorkshire Hull & East Yorkshire NHS Trust Peter Moss	16. St George's St George's University Hospitals NHS Trust Daniel Forton
6. West Yorkshire Leeds Teaching Hospitals NHS Trust Mark Aldersley	17. Surrey Hepatitis Services Royal Surrey County Hospital NHS Foundation Trust Michelle Gallagher
7. Lancashire and South Cumbria East Lancashire Hospitals NHS Trust Ioannis Glikas	18. Sussex Hepatology Network Brighton & Sussex University Hospitals NHS Trust Jeremy Tibble
8. Leicester University Hospitals of Leicester Martin Wiesla	19. Thames Valley Hep C ODIN Oxford University Hospitals NHS Trust Jane Collier
9. Birmingham University Hospitals Birmingham NHS Foundation Trust David Mutterer	20. Wessex Hep C ODIN University Hospital Southampton NHS Foundation Trust Mark Wright
10. Nottingham Nottingham University Hospitals NHS Trust Stephen Ryder	21. Eastern Hepatitis Network Cambridge University Hospitals NHS Foundation Trust William Gelson
11. London North West Imperial College Healthcare Trust Ashley Brown	22. West London
12. West London	23. Kent Network via Kings Kings College Hospital NHS Foundation Trust Kosh Agarwal
13. Paediatric Birmingham Women's & Children's Hospital NHS Foundation Trust Deirdre Kelly	24. National

# HCV and HIV Genomics Programmes

## Community Groups

e.g. Hep C Trust partnership,  
National AIDS Trust, HIV i-Base,  
THT

## Policy makers

e.g. Government,  
international bodies (WHO)

## Researchers

e.g. Academia, Industry

## National Surveillance Programs

- Genomics surveillance linked to HCV Registry & HARS
- Monitor progress to HIV transmission and HCV elimination



## Clinicians

Viral subtype, resistance, mixtures,  
recombinants, reinfections

## Public Health Practitioners

- Early outbreak identification
- Inform outbreak control team's action plan in real time

# Acknowledgements

## Antiviral Unit:

- Carmen Manso
- David Bibby
- Hodan Mohamed
- Juan Ledesma
- Renata Piorkowska
- Iona Christie
- Damayanti Prabhu
- Dulcibella Boampong
- Laura Phillips
- James Lester
- Daniel Kelly



## UKHSA

### Virus Reference Department

- Daniel Bradshaw
- Gary Murphy
- Christine Kelly

### Hepatitis Unit, BSHSH Division

- Ruth Simmonds
- Simon Parker
- Sema Mandal
- Sarah Arnold

### Pathogen Genomics Programme

### Central Sequencing Laboratory

### Data and Analytics Service

## UK HIV Drug Resistance Database

- David Dunn
- Deenan Pillay

## NIHR-HPRU in BBV & STI

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- William Rosenberg

## INITiO Surveillance Study

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- Alexandra Blenkinsop

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- Zena Lapp

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- Chris Nugent