

Sustained Drug-Resistant HIV-1 Lineages Circulate amongst Treatment-Naïve Individuals

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INTRODUCTION

- Between 50 and 70% of treated patients with virological rebound harbour some form of drug resistant virus in the UK [1]
- Transmitted drug resistance has reached up to 10% in areas of the world with access to treatment [2], and is assumed to reflect direct infection from drug-experienced individuals
- The contribution of untreated patients to the spread of drug resistance is unknown and the extent to which resistant HIV mutants may persist in a drug-naïve population in the absence of treatment has yet to be defined

AIM

Through the phylogenetic analysis of the largest UK database of HIV-1 sequences, we sought evidence of treatment-independent reservoirs of resistant viruses circulating amongst drug-naïve patients

METHODS

- 8,850 HIV-1 subtype B *pol* gene sequences (PR + RT; 1320 bp) were generated between 1997 and 2006 from drug-naïve (n = 4,870) and -experienced (n = 3,980) individuals
- The viruses' phylogeny was reconstructed by neighbor-joining inference, under the GTR + I + Γ model of evolution
- The evolutionary history of 37 resistance-associated codon positions [3] was reconstructed along the phylogenies by parsimony ancestral state reconstruction
- Lineages of drug-resistant viruses circulating amongst drug-naïve individuals were identified when resistance-associated polymorphisms were present at internal nodes linking > 3 patients with no known treatment history (Fig.1)
- The time of the most recent common ancestor of each drug-resistant lineage, corresponding to the date at which resistance mutations occurred in the clusters, was estimated using the Bayesian MCMC approach implemented in BEAST

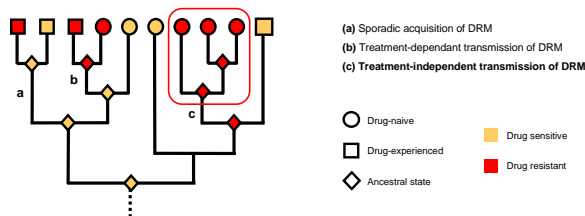


Figure 1. Schematic distributions of drug resistance mutations in the reconstructed HIV-1 *pol* gene phylogeny

RESULTS

Five treatment-independent drug-resistant lineages were identified, including 19, 9, 4, 3 and 3 patients respectively (Fig.2)

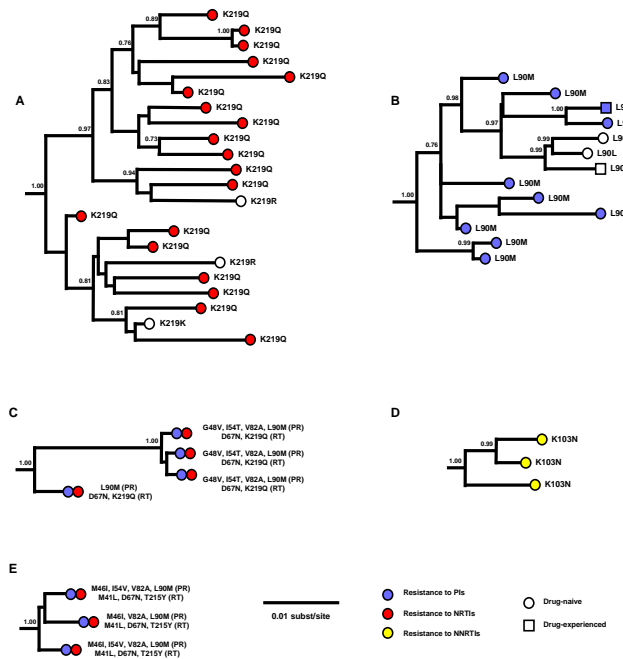


Figure 2. Phylogenies of the five resistant HIV-1 clusters circulating among drug-naïve individuals

Clusters A, B and D harboured mutations conferring resistance to a single class of antiretrovirals, while the two others exhibited genotypic resistance to more than one class of drugs

Table 1. Estimated time of origin of the five resistant lineages

Cluster	Root height*	95% HPD** lower	95% HPD upper	Model
A	1997.0	1995.7	1998.0	Relaxed clock
B	1998.3	1997.1	1999.4	Relaxed clock
C	1999.7	1997.4	2001.5	Relaxed clock
D	2001.2	1998.8	2003.2	Relaxed clock
E	2003.1	2001.8	2004.4	Relaxed clock

* Time of origin of the root of the cluster
** Highest posterior density

The estimated time of origin of the resistant lineages felt between 1997 [95% highest probability distribution: 1995; 1998] (cluster A) and 2003 [2001; 2004] (cluster E) (Table 1 and Fig. 3)

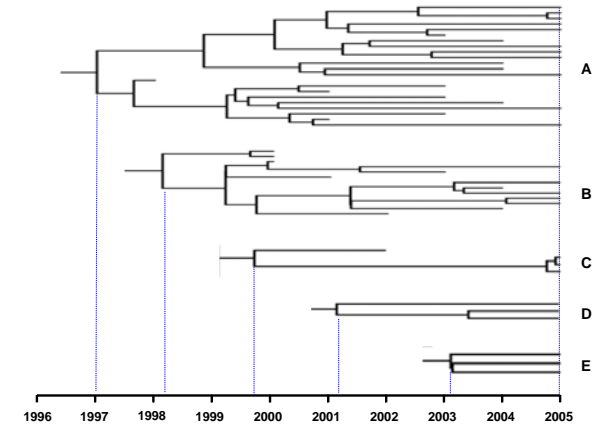


Figure 3. Estimated time of origin of the drug-naïve resistant viral clusters

CONCLUSIONS

- Five resistant HIV-1 lineages were identified amongst newly-infected individuals, indicative of treatment-independent reservoirs of resistance
- These lineages harbour mutations conferring resistance to the three main classes of antiretroviral drugs
- These lineages have persisted in the population for at least 2 years
- Given the current decrease in resistance transmitted from treated individuals, a greater proportion of resistance is likely to come from these reservoirs in the future

References

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