VIRUS EVOLUTION

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A1 The role of virus-antibody co-evolution in the development of a V3-glycan-directed HIV-1 broadly neutralizing antibody lineage

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Broadly neutralizing antibodies (bNAbs) are essential for a preventative HIV-1 vaccine but have not been elicited through vaccination. bNAbs develop in 20–30 per cent of HIV-1 infections and often target the V3-glycan epitope of the HIV envelope protein (Env). In these individuals, virus-antibody co-evolution is thought to drive the maturation of antibody lineages to neutralization breadth. We used deep sequencing of *env* genes and antibody transcripts from fourteen time points spanning the first 3 years of infection to characterize the virus-antibody co-evolution in donor CAP255 who developed V3-glycan-specific bNAbs. Sequencing and cloning of *env* genes, followed by neutralization assays, were used to identify Env mutations associated with neutralization escape from two bNAbs (CAP255.G3 and CAP255.C5) isolated at 149 weeks post-infection (wpi). Sequencing data indicated that CAP255 was co-infected by three related viral variants, all of which had an intact N332 glycan, which persisted in > 90 per cent of later viruses. A recombinant V3-region became fixed from 8 wpi, conferring slight neutralization resistance to CAP255.G3/C5 and other V3-glycan bNAbs. Later, T415R/K substitutions in V4 emerged by 51 wpi and were associated with complete viral escape from CAP255.G3/C5, though not from the polyclonal plasma response. All 93-week and later Envs were resistant to CAP255.G3/C5 and V3-glycan bNAb PGT135. Viral escape by 51 wpi suggested that the CAP255 bNAbs arose earlier, driving escape, but persisted to 149 weeks. This was supported by preliminary deep sequencing of the antibody repertoire that indicated bNAb lineage members were already present in the plasma at 39 wpi. Escape from V3-glycan bNAbs via T415R/K mutations have not previously been shown, suggesting a novel mode of recognition within the V3-glycan supersite. Further work will focus on identifying the bNAb-initiating Env and intermediate bNAb lineage members that were capable of engaging contemporaneous Env neutralization escape mutants. Characterization of Envs that engaged bNAb precursors, as well as those that selected for broader members of the bNAb lineage, will inform the design of immunogens capable of eliciting V3-glycan bNAbs in a novel HIV-1 vaccine regimen.

A2 Phylogenetic investigation of transmitted HIV-1 drug resistance mutations in Denmark, 2009–17

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Transmission of HIV-1 resistance mutations among therapy-naïve patients impairs the efficiency of antiretroviral therapy (ART). Therefore, genotypic resistance testing of patients is recommended at baseline, as this both allows for the selection of the correct ART regimen and for surveillance of transmitted drug resistance mutations (TDRM) among therapy naive HIV-1 patients. In Denmark, the occurrence of TDRM in newly diagnosed and therapy naïve HIV-1 patients is monitored through the SERO project. Here, we investigated if the prevalence of TDRM differed between patients within and outside of phylogenetically identified transmission clusters. Samples from 1,227 newly diagnosed HIV-1 patients were sent along with epidemiological information to the Virological Surveillance and Research group at Statens Serum Institut. HIV-1 RNA extraction, RT-PCR and Sanger sequencing of the *pol* gene was performed using an in-house assay. The sequences were analyzed using BioNumerics v. 6.6 and manually checked for the presence of mixed mutations and analyzed for mutations using the HIVDB 8.4 algorithm implemented at the Stanford database. Sequence alignments were performed in Mafft, and phylogenetic analysis was performed using Mega 6.0 using the Maximum likelihood general time reversible model with 100 bootstrap replicates. Clusters were identified with ClusterPicker at default settings (cluster support = 90%, genetic distance 4.5%). Active clusters contained newly diagnosed patients from the 2015 to 2017 period. HIV-1 sequences from 588 patients belonged to one of 154 clusters, and sequences from 639 patients did not belong to a cluster. Patients in clusters were significantly more likely to be men who have sex with men and subtype B and significantly less likely to be late presenters (Fisher's test $P < 0.05$). The TDRM prevalence was significantly higher for patients outside of clusters than within clusters, 16.6 per cent versus 12.1 per cent, respectively (Fisher's test $P < 0.05$); however, no significant differences were found in the TDRM prevalence between the 75 active and 79 inactive clusters, nor between small (<3 patients) and large (≥3 patients) clusters. E138A, V179D, and K103N were the three most prevalent TDRMs for both patient groups, whereas M41L differed between them. In Denmark, the TDRM prevalence is lower within clusters than outside, indicating that TDRM cases are either imported and/or belong to yet unidentified clusters.

A3 Molecular epidemiology of HIV-1 in Nigeria

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