The Influence of Host HLA on Antiretroviral Drug Resistance Mutation in HIV-1

Background
Antiretroviral (ARV) drugs select characteristic ‘drug escape’ mutations in HIV sequence. Host HLA-restricted anti-HIV CTL responses also select escape mutations in HIV-1.

We hypothesised that:
- Selection effects (current and primordial) of drugs and CTL responses are evident at a population level.
- Drug resistance mutations should be drug-specific and CTL escape mutations should be specific for HLA class I alleles.
- Drug pressure and CTL pressure may compete, leading to synergistic or antagonistic interactions.
- Such interactions may help explain variable rates of emergence of drug resistance between individuals, discordance of drug resistance patterns in-vitro and in-vivo and genotype/phenotype discordance.

Methods
HIV-1 RT and protease (proval DNA) sequencing in 492 subjects of the WA HIV Cohort, performed over 2300 person-years of observation, were analysed.

Polymorphism(s) (versus consensus) of each single AA residue across the pooled viral sequences of the cohort were determined.

We then carried out a multivariate analyses (logistic regression models using Epipop™ method) for each residue (eg 184 of RT) where: outcome= specified polymorphism (eg M184V, M184K) -covariates=ARV drugs and HLA-A-B alleles present in the population.

This process was repeated for all residues making up the full RT/protease proteins, giving a residue-specific view of the independent & interactive selection effects in-vivo of host CTL and ARV drugs on HIV-1, at a population level.

Conclusions
These findings support a highly dynamic, host-specific model of HIV-1 adaptation in-vivo, in which host CTL responses & ARV therapy act as concurrent, competing or parallel interacting evolutionary forces at the level of single viral residues.

The selection of characteristic drug resistance mutations (& expected associations with their causative drugs) are evident at a population level.

The selection of characteristic CTL escape mutations is also evident at a population level, as HLA allele-specific polymorphisms. These are present in drug treated individuals.

For 15 known drug resistance mutations in RT & protease, HLA alleles influence risk of having the mutation following drug therapy.

Better understanding of CTL-driven effects on HIV evolution prove useful for individualisation of ARV therapy.

References


[4] ABSTRACT
Background: Antiretroviral treatment (ART) induced mutations in HIV-1 reverse transcriptase (RT) and protease that allow viral escape from drug suppression are well characterised. Similarly, host CTL responses select viral variants that can escape CTL responses. We have shown in a large population study, that CTL escape mutations are evident as HLA allele-specific polymorphisms. These correlations are also found in vitro, using a panel of HIV-1 protease and RT variants with known HLA allele associations.

Results: Knowledge of characteristic HLA-specific effects on viral evolution and drug resistance may help explain variable susceptibility to drug resistance and be useful for individualised therapy. This process was repeated for all residues making up the full RT and protease proteins, giving a residue-specific view of the independent & interactive selection effects of host CTL and ARV drugs on HIV-1, at a population level.