Potential impact of differences in frequency of minor substitutions between HIV-1 subtypes on the genetic barrier for resistance to protease inhibitors


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Background – The number of minor protease substitutions in wild-type virus at positions targeted during antiretroviral drug treatment, varies considerably between HIV-1 subtypes. Minor protease substitutions by themselves do not impair drug susceptibility but might enhance resistance by improving the replicative capacity of the resistant virus. Therefore, the subtype naturally containing the largest number of minor protease substitutions could have a lower genetic barrier for drug resistance. In this study, the number of minor protease substitutions for every protease inhibitor (PI) was compared between subtypes using almost 2000 sequences from antiretroviral-naïve patients.

Methods – Identified were subtypes A to G, J, CRF01_AE and CRF02_AG. The most common clade was B (1299 sequences). Among the 556 sequences classified with a non-B subtype, C (n=209) and G (86) were the most frequent. The relevant minor substitutions were obtained for every PI from the IAS-USA list of 2004. The frequency of minor protease substitutions was compared between sequences of clade B and all individual non-B subtypes using almost 2000 sequences from antiretroviral-naïve patients.

Results – The sequences of non-B subtype had 20% (subtypes C, D and CRF01_AE) to 70% (G, J, CRF02_AG) more minor protease substitutions as compared to clade B (p<0.001). All individual non-B subtypes contained on average more minor substitutions specific for indinavir, nelfinavir, atazanavir and ritonavir (p<0.001). Conversely, subtype B sequences generally harboured more minor protease substitutions relevant for amprenavir, saquinavir, lopinavir/ritonavir and tipranavir (p<0.001). Specifically, non-B sequences contained relatively more often the K20R (generally >15% for most non-B sequences versus 2% in B; p<0.001), and M36I substitutions (>85% in non-B and 17% in B; p<0.001). On the other hand, L63P (9-30% of non-B, 57% of B), and V77I (0% to 15% in individual non-B, 27% of B) were found more frequently in subtype B sequences (p<0.001).
**Conclusion** – Sequences of all individual non-B subtypes contain in general more minor protease substitutions. Whether these differences in frequency of minor substitutions between subtypes are associated with dissimilarities in the genetic barrier remains to be investigated. If confirmed, such differences should be taken into account in the initial choice of antiretroviral drug regimens.