Journal of the International AIDS Society

Poster presentation

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Reduced susceptibility to lamivudine and emtricitabine associated with the novel K66N mutation in HIV-1 reverse transcriptase

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from Ninth International Congress on Drug Therapy in HIV Infection
Glasgow, UK. 9–13 November 2008

Published: 10 November 2008

Journal of the International AIDS Society 2008, **11**(Suppl 1):P187 doi:10.1186/1758-2652-11-S1-P187

This abstract is available from: http://www.jiasociety.org/content/11/S1/P187

Background

Discrepancies between results obtained in phenotypic drug resistance tests and genotype or phenotype interpretation algorithms often lead to the recognition of important resistance associated mutations. The drug resistance profile of K66N, a novel mutation in HIV-1 reverse transcriptase (RT) was identified as a result of discrepant phenotype/genotype results.

Methods

A recombinant clinical isolate from a patient failing his antiretroviral treatment harboring the K66N and D67G (1) mutations in RT had reduced susceptibility for lamivudine (3TC) and emtricitabine (FTC) in a phenotypic assay (Antivirogram®), while the genotype interpretation algorithms (Virco® TYPE-HIV-1, Stanford & ANRS) showed a susceptible profile for 3TC and FTC. The mean fold-change (FC) values in the phenotypic assay (Antivirogram®) were 6.2 for 3TC and 22.1 for FTC (2 measurements each). A HIV-1 HXB2 site-directed mutant (SDM) harboring K66N in the RT was tested in the phenotypic assay. The Virco database was searched for isolates harboring K66N.

Summary of results

The FC values of SDM K66N in the phenotypic assay were 5.3 and 4.9 for 3TC and FTC, respectively (mean of four measurements each). Antivirogram® biological cut-offs for 3TC and FTC are 2.1 and 3.0, respectively. The K66N mutation was found to be rare, occurring in 0.026% of queried sequences (77/292.910); 44% of the K66N isolates found in the database harbored the mutation as a mixture with the wild-type amino acid, while approximately 52% of all isolates with K66N had a pure K66N mutation.

Conclusion

The mutation K66N in HIV-1 RT is associated with reduced phenotypic susceptibility to 3TC and FTC. Further research is required to investigate the clinical impact of this finding, how the mutation evolves and whether it is selected during a specific therapy.

References

1. Richard N, *et al.*: *Antimicrob Agents Chemother* 2000, **44:**1127-31.