Journal of the International AIDS Society

Poster presentation

Are non-B subtypes less susceptible to antiretroviral drugs? A bioinformatical approach to prediction of non-B subtype susceptibility

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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):P183 doi:10.1186/1758-2652-11-S1-P183

This abstract is available from: http://www.jiasociety.org/content/11/S1/P183

Background

The first generation antiretrovirals that have been developed and used to treat primarily subtype B infected patients are finally becoming available in African countries. However, the subtype B is not the dominant subtype in Africa and the question remains if these subtypes are susceptible to these drugs. We will here try to answer this question by use of artificial neural networks (ANNs). We have previously showed that, based on the physiochemical properties of the amino acids, ANNs are able to extrapolate predictions to non-B subtypes with high accuracy [1].

Methods

We applied the use of these ANNs to further predict the IC50 FC susceptibility for the most dominant subtypes in Africa: A, C, G and CRF_AG; to the drugs: abacavir, amprenavir, atazanavir, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, tenofovir, zalcitabine, zidovudine. We obtained reference sequences for these subtypes from the Los Alamos HIV sequence database. These subtypes we used for input to the ANNs to predict the IC50 FC for each of the above drugs. We used an unpaired t-test to identify significant differences in mean of the IC50 FC values between B-subtype and non-B subtypes.

Summary of results

Plots of the predictions for the individual drugs and mean for each subtype is shown in Figure 1. We found no significant difference in mean IC50 FC for subtypes C (mean = 0.74) or CRF_AG (mean = 0.87) compared to the subtype B (mean = 1.02). But there was a significant difference between B and A (mean = 1.18) and B and G (mean = 1.31). Drugs with a predicted IC50 FC >2-fold are for A: zidovudine: 2.7 and nelfinavir: 2.4; C: nelfinavir 3.2; G: amprenavir: 2.2, zidovudine: 2.5, nelfinavir: 4 and atazanavir 4.1; CRF_AG: atazanavir: 2.5, zidovudine: 2.8 and nelfinavir 3.2. Excluding these drugs from the analysis resulted in all differences in mean IC50 FC between subtype B and non-B subtypes not to be significant.

Conclusion

Predictions showed significant difference between the predicted mean IC50 FC values for the both A and G HIV-1 subtypes compared to IC50 FC for subtype B. This is in large driven by reduced susceptibility to amprenavir, atazanavir, nelfinavir, and zidovudine and does also affect susceptibility for C and CRF_AG subtypes. With the majority of the drugs we did not find any reduced susceptibility for the subtypes.

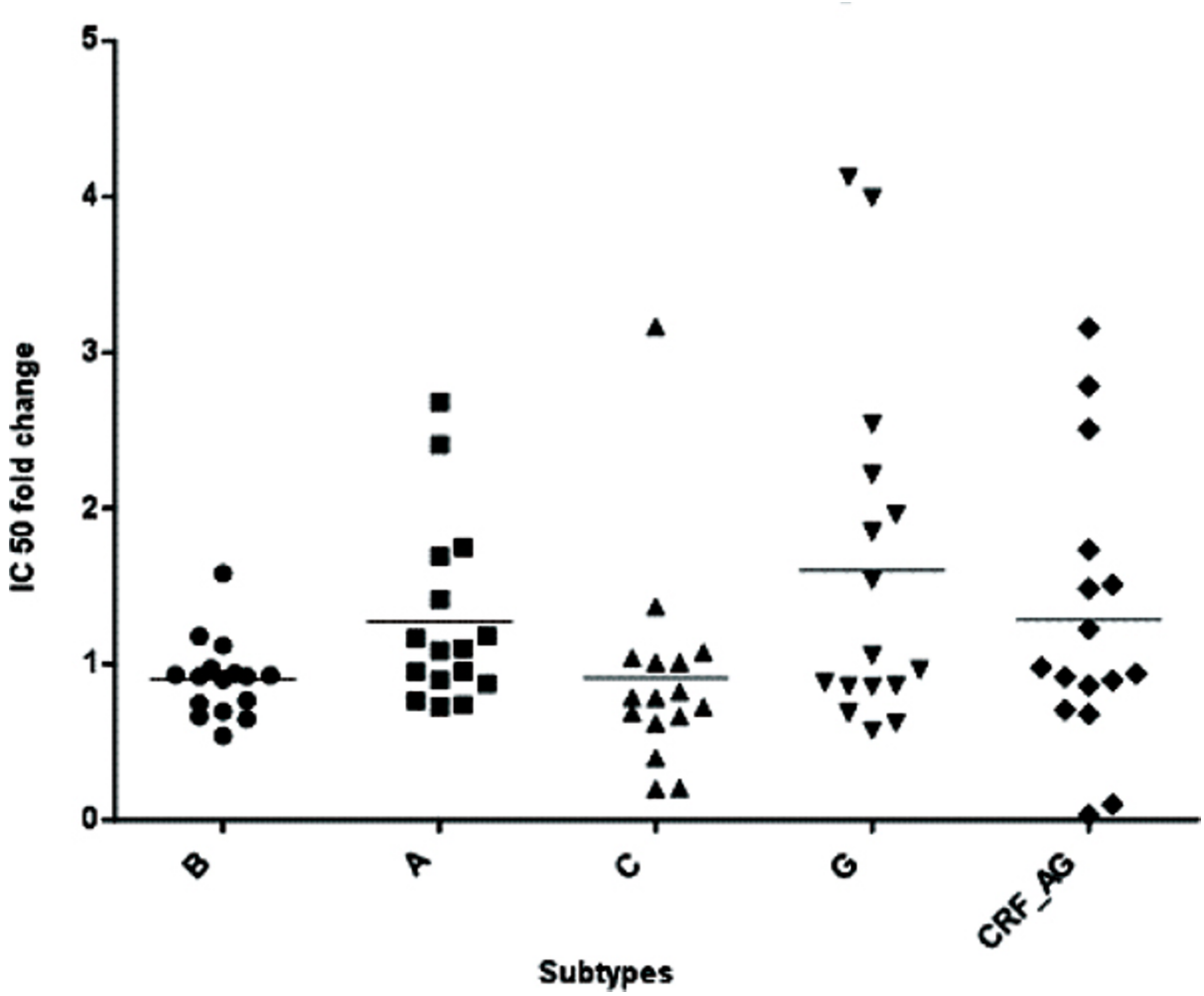

Figure 1
Predicted IC50 fold change.

References

1. Kjær J, *et al.*: **Prediction of phenotypic susceptibility to antiretroviral drugs using physiochemical properties of the primary enzymatic structure combined with artificial neural networks.** *HIV Med* . 2008 (July 2)