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# Protease inhibitor-induced cardiotoxicity: direct effects on cell viability and intracellular calcium levels

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## Purpose of the study

Long-term use of protease inhibitors (PIs) is associated with increased cardiovascular risk linked to metabolic imbalance and endothelial dysfunction. The direct effects of PIs on cardiomyocytes have not been studied, but may be critical to our understanding of the cellular mechanisms contributing to ART-associated cardiovascular dysfunction in HIV patients. This study aims to assess the effects of antiviral agents on cell survival and intracellular calcium levels in cardiomyoblasts (H9c2).

## Methods

H9c2 cells were cultured and incubated in medium supplemented with 10% FCS and antibiotics at 37°C (5% CO2). Cells were incubated in medium supplemented with RTV (Ritonavir), TFV (tenofovir), NFV (nelfinavir), IDV (indinavir), NVP (nevirapine), SQV (saquinavir), EFV (efavirenz) or FOS (fosamprenavir) for 24 hrs (0.01–50 μM). DMSO and doxorubicin were controls. Cells were stained with Hoechst and Fluo-4, and analysed by high throughput fluorescence microscopy (INcell 1000, GE). Data were analysed by ANOVA with post hoc analysis (Dunnetts) or Student-t test, and expressed as mean ± s.e.m.

## Summary of results

RTV, NFV, SQV and EFV dose dependently decreased cell survival. At a concentration of 10 μM, cell survival was decreased ($p < 0.05$) by 44.3 ± 8.7% (NFV), 36.4 ± 11.2% (EFV), 35.1 ± 3.2% (SQV) and 18.0 ± 2.1% (RTV); other drugs had minimal effect. The combination of SQV/RTV (clinical concentrations) reduced cardiomyoblast survival compared to untreated cells (76.7 ± 5.7% vs 100 ± 5.2%; $p < 0.05$). NFV increased intracellular calcium levels to 300 ± 30% ($p < 0.05$) at a concentration of 10 μM and above, which is comparable to that observed with DOX (450 ± 75%). The other drugs had little effect on intracellular calcium levels.

## Conclusion

In conclusion, SQV, NFV EFV and RTV are cardiotoxic in this cell line. Only NFV altered intracellular calcium levels. The effects on cell survival and intracellular calcium levels are likely to have functional consequences with regard to cardiac contractility and intracellular signalling mechanisms. Furthermore, this assay is suitable for high content screening of new drugs.