HERV-K Env Upregulation in Lymphoma Cells Under Antiretroviral Chemotherapeutic Exposure

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BACKGROUND

Endogenous retroviruses (ERVs) have a potential regulatory and pathogenic role in cancer. Antiretrovirals agents have been reported to influence HERV activity, but little is known about their interactions with classical chemotherapeutics. We investigated whether antiretrovirals Dolutegravir (DTG) and Doravirine (DOR) alter HERV-K expression and cytotoxic responses to Doxorubicin (D) and Vincristine (V) in lymphoma cell lines (BJAB & L428).

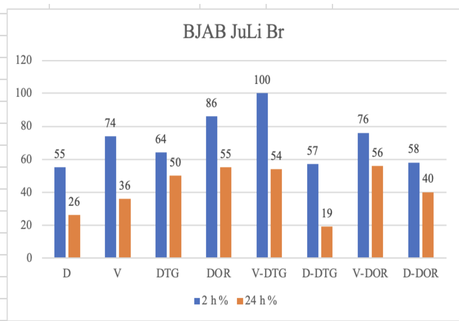
METHODS

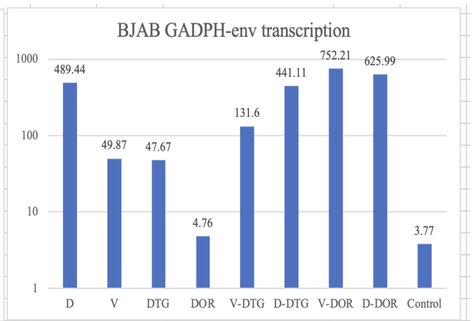
HERV-K *env* & *gag* expression was quantified with RT-PCR. Expression was normalized to β-actin & GADPH. A change of >10 times was considered significant. IC_{50} values for DTG, DOR, D & V were determined with MTT. Chemotherapeutics were administered at IC_{50} & antiretrovirals were administered at IC_{20}. Cell viability was measured with JuLi Br at the 2nd & 24th hours. Cells were grouped as early apoptosis (EA), late apoptosis (LA) and necrosis (Nec) with Annexin V staining.

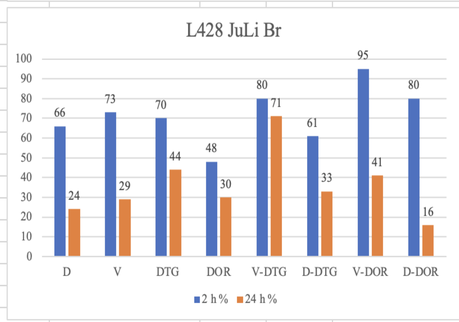
In our study, the V+DTG group created a significant increase in HERV-K env expression which was correlated with an increase in late apoptosis and a decrease in cell death. This shows that Dolutegravir and Doravirine influence how lymphoma cells respond to chemotherapeutic drugs by modulating the expression of HERV-K *env.*

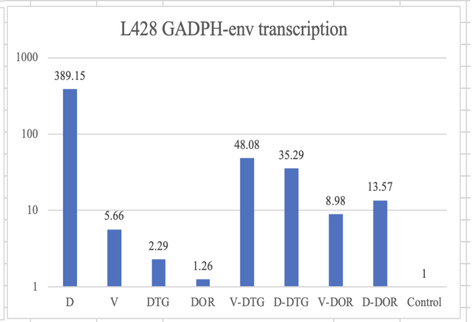
RESULTS

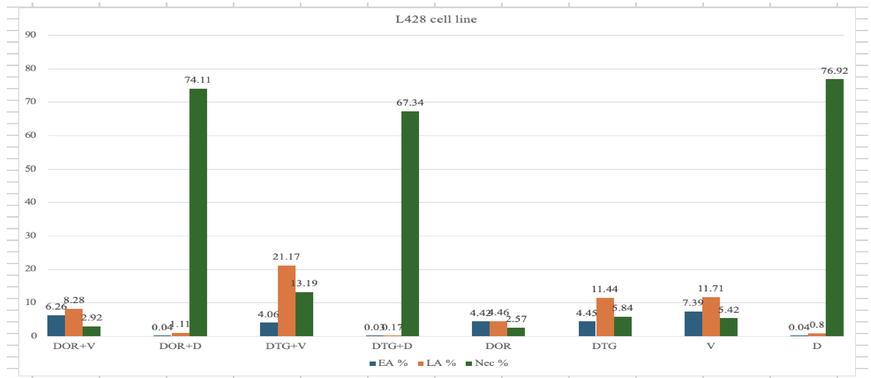
IC50 for DTG 3.733 mM (L428), 25.31mM (BJAB); DOR 0.642 mM (L428), 0.778 mM (BJAB). IC50 for D 0.552 mM (L428), 0.496 mM (BJAB); for V 0.22 mM (L428) & 0.237 mM (BJAB). The IC20 of antiretrovirals: for DTG 2.78 mM (L428), for DOR 0.52 mM (L428); DTG 15.4 mM (BJAB), & DOR 0.45 mM (BJAB). Combination groups enhanced HERV-env expression relative to single drugs. Exposure to D induced the highest increase in HERV-K expression (between 400-3000 times). V+DTG increased env expression of 50 times in L428 cells, more than either agent alone. Overall, JuLi Br assay showed a progressive loss of viable cells. V+DTG caused 9% decrease in L428 cells, less than either agent separately. In the Annexin V assay, the L428 groups containing D almost exclusively resulted in necrosis, and the L428 V-DTG group showed an increase in late apoptotic cells compared to V or DTG alone.

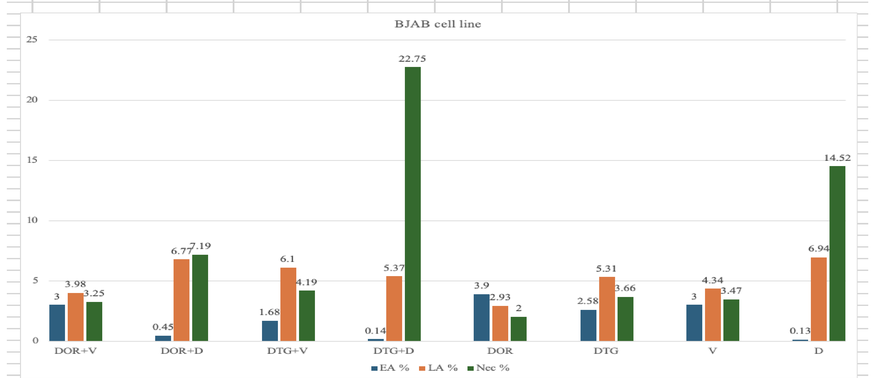












CONCLUSIONS

Chemotherapeutics, especially D, strongly upregulate HERV-K *env* in lymphoma cells, and antiretrovirals further modulate this response. The observed links between drug-induced stress, endogenous retroviral activation, and cell death mechanisms highlight a potential role for HERV-K in therapy response and resistance. These findings support further investigation of HERV-K as both a biomarker and a therapeutic target in lymphoma.

PLAIN LANGUAGE SUMMARY

Endogenous retroviruses (ERVs) are a group of elements in our genome that have a role in the development in cancer. In this study we show that drugs used in the treatment of HIV can interact with chemotherapy drugs to influence the proliferation of lymphoma cells, highlighting a potential use ERVs in cancer treatment.

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