Regulation of Telomerase Activity in PBMCs Exposed to Antiretroviral Drugs

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Background

► Telomere attrition is one of the hallmarks of aging. However, it is unknown if this mechanism contributes to accelerated aging in HIV infected patients.

► One single prior study has shown that tenofovir (TFV), abacavir (ABC), lamivudine (3TC) and emtricitabine (FTC) inhibited telomerase activity in vitro in activated peripheral blood mononuclear cells (PBMCs). However, only TFV inhibited telomerase activity at therapeutic concentrations (1).

► Two studies have shown that saquinavir increased telomerase activity in activated PBMCs (2, 3).

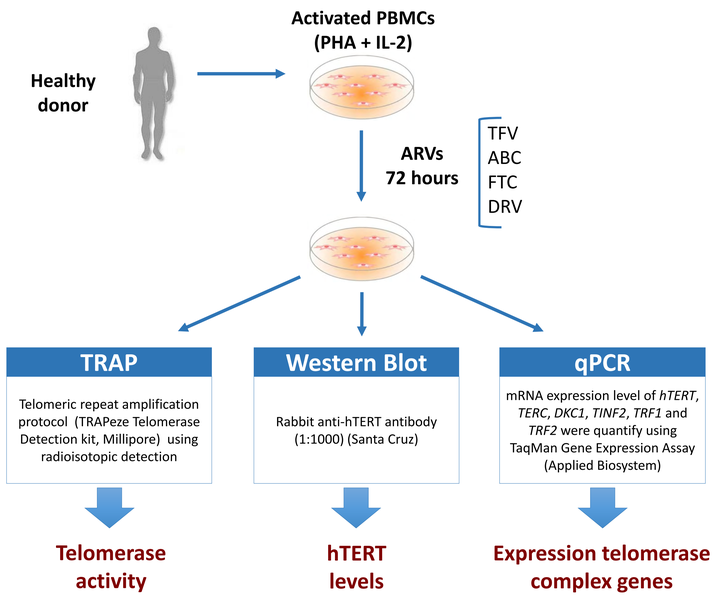
Objectives

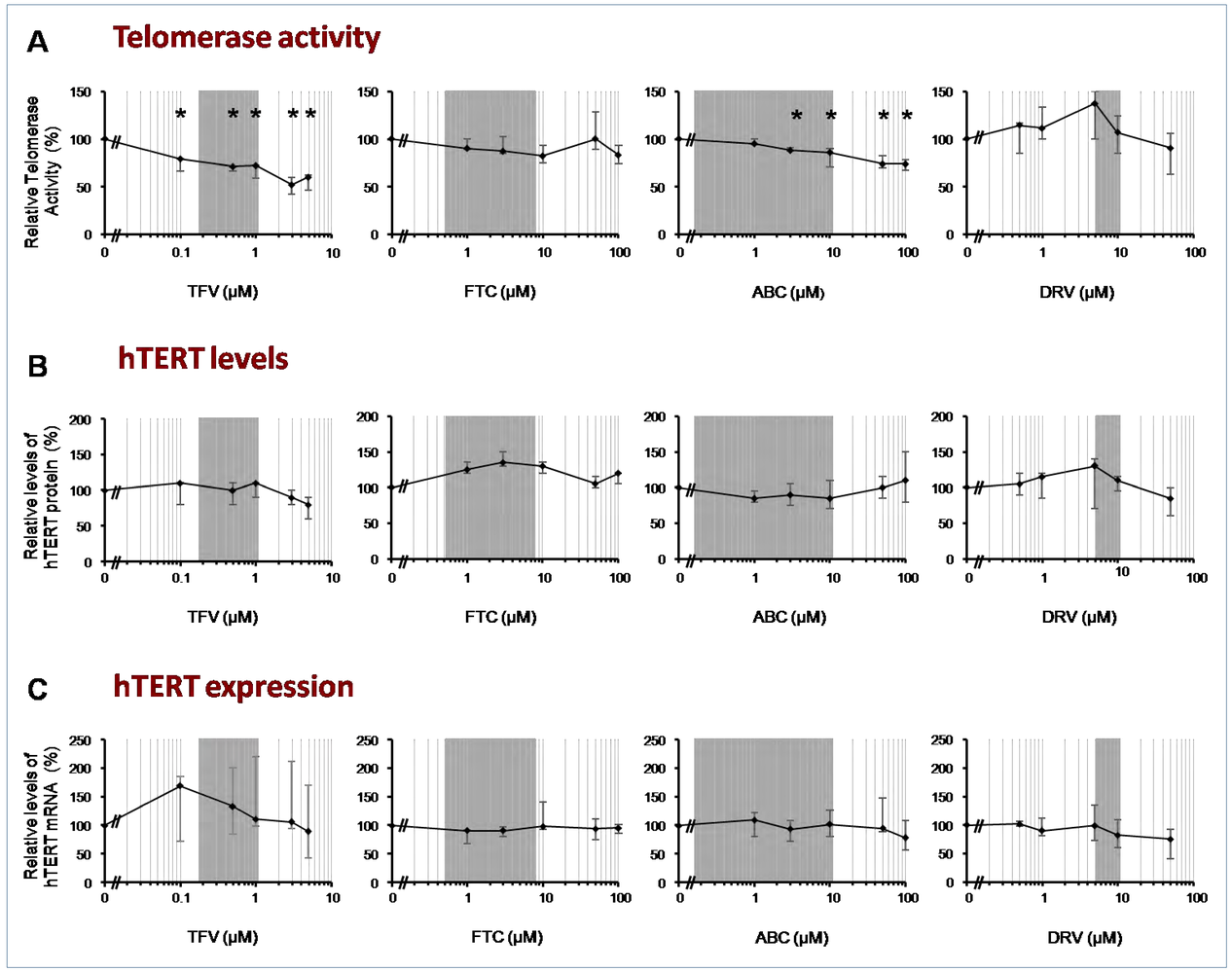
► To confirm if therapeutic concentrations of ABC, FTC and especially TFV inhibit telomerase activity in vitro in activated-PBMCs.

► To assay whether darunavir (DRV) has an impact on telomerase activity.

► To evaluate the possible impact of these antiretrovirals (ARVs) on expression of telomerase genes.

Methods





The effect of nucleos(t)ide reverse transcriptase inhibitors (n=5) and darunavir (n=6) on telomerase activity (A), levels of hTERT protein (B) and hTERT mRNA (C) in activated PBMCs. Concentrations used for ABC and FTC were 0; 1; 3; 10; 50 and 100 µM, for TFV were 0; 0.1; 0.5; 1; 3 and 5 µM and for DRV were 0; 0.5; 1; 5; 10; 50 µM. Close circle represent the median, error bars represent interquartile range and gray bars represent the expected plasma levels in vivo for each antiretroviral (boosted DRV therapeutic range was assumed for DRV). Data show percentage of telomerase activity, levels of hTERT protein and amount of hTERT mRNA of untreated cells.

$*$ $p < 0.05$

Conclusions

► Our results suggest that TFV and ABC but not FTC or DRV, inhibit telomerase activity within the therapeutic range.

► This inhibition does not involve changes in expression levels of telomerase genes or hTERT protein.

► The in vivo relevance of these findings remains to be elucidated.

Results

► **TFV and ABC inhibit telomerase activity in vitro**

TFV and ABC induced a significant dose-dependent decrease of telomerase activity within the therapeutic concentration range. Median inhibition induced by TFV at 0.5 µM and 1 µM was 29% (IQR: 29%-34%; range: 12%-39%; p=0.042) and 28% (IQR: 28%-41%; range: 25%-47%; p=0.042), respectively. For ABC at 3 µM and 10 µM median inhibition was 12% (IQR: 9%-13%; range: 8%-17%; p=0.043) and 14% (IQR: 10%-29%; range: 7%-40%; p=0.043), respectively. Exposure to FTC or DRV did not affect telomerase activity even at concentrations above the therapeutic plasma level range (Figure A).

► **No changes in levels of hTERT protein**

We did not find differences in the amount of hTERT between untreated and treated PBMCs (Figure B).

► **No changes in expression of the telomerase complex genes**

We did not detect changes in expression of the gene that code for the catalytic subunit of the telomerase complex (hTERT) (Figure C) or other telomerase complex genes (data not shown).

References

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