THE SAFETY AND EFFECT OF MULTIPLE DOSES OF VORINOSTAT ON HIV TRANSCRIPTION IN HIV-INFECTED PATIENTS RECEIVING COMBINATION ANTIRETROVIRAL THERAPY

Julian Elliott[1,2,3], Ajantha Solomon[2,3], Fiona Wightman[2,3], Miranda Smith[2,3], Sarah Palmer[4], Miles Prince[5], Jo Watson[6], Jennifer Hoy[1,2], James McMahon[1,2], Sharon R Lewin [1,2,3]

[1]Alfred Hospital, [2]Monash University and [3]Burnet Institute, Melbourne, Australia; [4]Karolinska Institute, Sweden; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]National Association of People Living with HIV, Sydney, Australia

Background: The histone deacetylase inhibitor, vorinostat, activates HIV transcription from latently infected CD4+ T-cells. The aims of this study were to determine (i) the safety and tolerability of multiple doses of vorinostat in HIV-infected patients on combination antiretroviral therapy (cART) and (ii) the effect of daily dosing on HIV transcription in CD4+ T-cells in blood and rectal tissue.

Methods: HIV-infected adults on suppressive cART (n=20) were enrolled in a prospective single arm study and received vorinostat 400 mg once daily for 14 days. Blood was collected at 0, 2, 8 and 24 hours, and 7, 14, 21, 28 and 84 days. Rectal biopsies were performed at day 0 and 14. Cell associated unspliced (CA-US) RNA and HIV DNA were quantified in CD4+ T-cells from blood (n=17) and rectal tissue (n=10). Significant changes in CA-US RNA and HIV DNA were determined using paired t-tests for intra-patient change; and Wilcoxon signed rank test and generalized estimating equations (GEE) for group analyses.

Results: Median baseline CD4 count was 721 (range 371 – 1335) cells/μl and duration of virus suppression was 5.0 (range 2.7 – 13.4) years. Grade 1 or 2 adverse events occurred in 90% (18/20) of patients, most commonly nausea, diarrhoea, fatigue and thrombocytopenia. There were no higher grade adverse events, dose modification or drug discontinuations. One participant had a transient increase in plasma HIV RNA while on vorinostat (peak HIV RNA=160 copies/ml). All other participants maintained plasma HIV RNA <20 copies/ml throughout follow up. A significant increase in CA-US RNA occurred in 88% (15/17) of participants during vorinostat dosing. CA-US RNA in blood increased significantly by 8 hours after first dose and remained elevated throughout follow up, including the period after vorinostat ($p<0.001$ for all time points). Compared to baseline, mean fold change in CA-US RNA during vorinostat was 2.53 (95% CI, 1.11-3.01, $p=0.029$) and after vorinostat was 2.78 (95% CI, 1.26-3.91, $p=0.008$). There were no significant changes in HIV DNA in all analyses. In CD4+ T-cells from rectal tissue, there was a trend to an increase in CA-US RNA ($p=0.08$) but no change in HIV DNA ($p=0.59$).

Conclusion: Multiple doses of vorinostat were safe, well tolerated and induced a sustained increase in CA-US RNA in CD4+ T-cells. Fourteen days of vorinostat was not associated with any change in HIV DNA suggesting additional strategies will be needed to eliminate latently infected cells.