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NO RESIDUAL VIRUS REPLICATION IN A RANDOMISED TRIAL OF DOLUTEGRAVIR INTENSIFICATION
Basic Science: (D) HIV Reservoirs, Latency, and All Curative Strategies Including Therapeutic Vaccines and Gene Therapy
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Background: Whether residual virus replication (RVR) persists in HIV-infected individuals on suppressive antiretroviral therapy (ART) remains controversial. One strategy used to demonstrate RVR is to intensify ART with an integrase inhibitor and measure an early increase in 2-long terminal repeat (2-LTR) circles. Two previous studies with raltegravir demonstrated RVR in a subset of individuals on ART. Here we investigated the effects of dolutegravir.
Methods: In a randomised, placebo-controlled, double-blinded clinical trial, HIV-infected adults with virological suppression for >3 years were randomly assigned 1:1 to dolutegravir 50 mg or placebo daily for 56 days in addition to background ART. The primary outcome measure was the level of 2-LTR circles in CD4+ T cells at day 7. Cell-associated unspliced (CA-US) HIV RNA, total and integrated HIV DNA, and plasma HIV RNA using a single copy assay (SCA) were quantified by real-time PCR; T cell expression of HLA-DR, CD38 and PD-1 by flow cytometry, and plasma levels of interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), d-dimer and soluble CD14 (sCD14) by ELISA. We used repeated-measures analysis of variance (ANOVA) as the protocol-defined primary analysis. Student's t-test or rank sum test, were used to compare changes from baseline to specific time points across study arms.
Results: We enrolled 40 HIV-infected individuals; 21 were allocated to dolutegravir and 19 to placebo with 14 and 11% receiving a protease-inhibitor based ART regimen respectively. All participants completed the study. There was no significant difference in the primary endpoint, 2-LTR circles in peripheral blood CD4+ T cells, as assessed by repeated-measures ANOVA over 7 days (p=0.17) or any other time point (Figure). Median (IQR) 2-LTR circles fold-change from baseline to day 7 was -0.17 (-0.90 to 0.90) in the dolutegravir and -0.26 (-1.00 to 1.17) in the placebo groups. We found no consistent difference in the levels of CA US HIV-RNA, total and integrated HIV DNA (Figure), SCA, T cell activation markers or plasma levels of sCD14, d-dimer, IL-6 or hs-CRP. PD-1 expression in CD4+ T cells declined slightly after 56 days in placebo recipients compared to dolutegravir (p=0.03).
Conclusion: In a randomised, double-blinded, placebo-controlled trial of dolutegravir intensification, there was no evidence of RVR on ART.