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IMPACT OF RALTEGRAVIR INTENSIFICATION OF FIRST-LINE ART ON IRIS IN THE REALITY TRIAL

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Background: Among HIV-infected adults/children with CD4<100 cells/ul initiating ART in sub-Saharan Africa, the REALITY trial (ISRCTN43622374) showed that 12-week raltegravir (RAL)-intensified quadruple therapy resulted in significantly faster VL declines through 24 weeks, but did not reduce overall mortality or WHO 3/4 events compared to standard triple-drug ART. Integrase inhibitors may replace NNRTIs in first-line ART; there is concern that more rapid VL declines may lead to higher rates of serious IRIS in severely immunocompromised individuals starting ART.
Methods: ART-naïve HIV-infected adults/children ≥5y with CD4<100 cells/ul were randomized to initiate ART (2NRTI+NNRTI) with 12 weeks RAL (Std+RAL) or without (Std). Events, causes of death, and compatibility with IRIS were adjudicated by an endpoint review committee blind to randomization. Predictors of time to first fatal/non-fatal IRIS-compatible event were identified using backwards elimination treating death from other causes as a competing risk.
Results: 1805 patients with median baseline CD4 37 cells/ul and VL 249770 c/ml (74.0%≥100,000c/ml) were randomized to Std+RAL (n=902) vs Std (n=903). Mean change in log10 VL at week 4 was –3.4(SE 0.03) in Std+RAL vs -2.7(0.03) in Std (p<0.001; 42.8% vs 14.5% <50 c/ml respectively). In total 67(29.8%) of 225 deaths were adjudicated as IRIS-compatible, occurring a median 4.4(IQR2.6-9.4) weeks after ART initiation; a further 113 non-fatal IRIS-compatible events occurred after median 3.4(2.0-6.3) weeks on ART (figure). Fatal/non-fatal IRIS-compatible events occurred in 89(9.9%) Std+RAL vs 86(9.5%) Std patients (p=0.79). TB-IRIS occurred in 53(5.9%) vs 54(6.0%) respectively (p=1.00), cryptococcal-IRIS in 15(1.7%) vs 16(1.8%) (p=1.00), other IRIS events of known aetiology in 17(1.9%) vs 14(1.6%) (p=0.59) (Kaposi's sarcoma (8 vs 4), viral hepatitis (1 vs 3), CNS event unknown pathogen (3 vs 1), CMV (2 vs 1), toxoplasmosis (1 vs 1), PCP (0 vs 2), lung event unknown pathogen (0 vs 2), and other (3 vs 0)), and IRIS events of unknown aetiology in 4(0.4%) vs 2(0.2%) respectively. Risks of non-fatal/fatal IRIS were independently higher in those with lower pre-ART CD4 (p<0.001), older individuals (p=0.004) and those with TB at ART initiation (p=0.01).
Conclusion: Despite significantly more rapid declines in HIV VL, there was no evidence that 12 weeks' RAL intensification impacted incidence or case-fatality of IRIS in severely immunocompromised individuals initiating ART.