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SAFETY & PK OF WEEKLY RIFAPENTINE/ISONIAZID (3HP) IN ADULTS WITH HIV ON DOLUTEGRAVIR

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Background:

Short-course preventive therapy with 12 once-weekly rifapentine/isoniazid doses (3HP) could transform TB control, but drug interactions with antiretrovirals may pose implementation challenges. In a previous trial, 3HP administered with dolutegravir (DTG) resulted in serious adverse events (AE) in 2/4 healthy subjects (fever, hypotension, elevated transaminases); the study was halted. We conducted a Phase I/II study of 3HP and DTG in adults with HIV to characterize safety, drug interactions, and viral suppression.

Methods:

HIV infected adults with undetectable viral load on efavirenz (EFV)-based regimens were recruited into 3 groups. All received DTG in place of EFV for 8 weeks, then began 3HP; after 3HP completion, all participants were followed 4 more weeks. Viral loads were measured at baseline and weeks 11 and 24. Groups 1A (n=12) and 1B (n=18) had intensive DTG PK sampling performed at week 8 (pre-HP), then weeks 11 and 16 following the 3rd and 8th doses of HP. Group 2 (n=30) were treated with the same schedule and had sparse DTG PK sampling at weeks 8, 11 and 16. Primary endpoints were 1) grade >3 AE and 2) population PK parameters of DTG with or without HP. An independent Study Monitoring Committee recommended release of results following its second review.

Results:

Of the 60 participants who received 3HP, 43 (70%) were female, median (IQR) age was 40 (35-48) years, all were black African, median (IQR) CD4 was 683 (447-935) cells/mm³, and median (IQR) BMI was 28.9 (24.0-32.9) kg/m². All participants received ≥6 HP doses at the time of this report. Three Grade 3 AE occurred (2 elevated creatinine, 1 hypertension). HIV viral loads at baseline, day 58 (pre-HP), day 72 (3rd HP dose) and day 168 (post-HP) were all <40 c/mL. Table 1 shows Group 1A and 1B PK results. The geometric mean (GM) trough concentration of DTG on Day 58 (pre-HP) was 1003 ug/mL (5th-95th %ile: 500-2080), and during HP treatment 546 (134-1616) with all trough levels but one above DTG IC₉₀ of 64 ug/mL; Table). Overall, HP administration decreased DTG bioavailability by 29% (RSE 13%) (+18%, -37% and -35% for week 1, 3 and 8), while clearance remained unchanged.

Conclusion:

Co-administration of DTG and HP was well-tolerated, with no HP-related Grade >3 AEs. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC₉₀. All viral loads were suppressed. DTG may be co-administered with 3HP without dose adjustment.