Neurotoxicity with high dose disulfiram and vorinostat used for latency reversal

McMahon JH1, Evans V2, Lau JSY1, Solomon A2, Tennakoon S2, Dantanarayana A2, Hagenauer M1, Lee S3, Palmer S4, Fisher K4, Pumpus N1, Burger D6, Wu G7, Howell BJ7, Rasmussen TA2, Lewin SR1,2

1) Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia; 2) The Peter Doherty Institute for Infection and Immunity, University of Melbourne and Royal Melbourne Hospital, Melbourne, Australia; University of California San Francisco, San Francisco; 3) California, United States; 4) The Weizmann Institute for Medical Research, University of Sydney, Weizmann, Australia; 5) Johns Hopkins University, Baltimore, Maryland, United States; 6) Department of Pharmacy, Radboud University Medical Center, the Netherlands; 7) Department of Infectious Disease Merck & Co. Inc., Kenilworth, New Jersey, USA; 8) Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark

ART, VOR and DSF were detectable in participant samples and DSF in participant 59. Plasma concentrations of ART, VOR, and DSF were used to treat alcohol dependence, reverse HIV latency in vivo by different pathways and have been safely studied in people with HIV.1,2

In a prior study, three days of 2000mg DSF was well tolerated and led to an approximate 2 fold increase in plasma HIV RNA.3,4

Neurotoxicity (forgetfulness, ataxia, delirium, psychosis) has been associated with DSF use.5,6

Drug interactions between DSF and VOR have not been reported and are not expected based on the reported mechanisms of absorption, metabolism and elimination.7

This study aimed to determine whether the combination of DSF and intermittent VOR in HIV-infected individuals on ART: increased the potency of latency reversal; was safe and tolerable.

RESULTS

**Participant 1**

- **Day 196**: ABC 0.248, TAC 1.52
- **Day 37**: ABC 0.222, TAC 0.937
- **Day 21**: ABC 0.292, TAC 0.326
- **Day 15**: ABC 0.343, TAC 0.130
- **Day 10**: ABC < 0.015, TAC < 0.015
- **Day 5**: ABC < 0.015, TAC < 0.015
- **Day 4**: ABC < 0.015, TAC < 0.015
- **Day 3**: ABC < 0.015, TAC < 0.015
- **Day 2**: ABC < 0.015, TAC < 0.015
- **Day 1**: ABC 0.238, TAC 0.518
- **Day 8**: ABC 0.295, TAC 0.335
- **Day 11**: ABC 0.48, TAC 0.427

**Participant 2**

- **Day 196**: ABC 0.248, TAC 1.52
- **Day 37**: ABC 0.222, TAC 0.937
- **Day 21**: ABC 0.292, TAC 0.326
- **Day 15**: ABC 0.343, TAC 0.130
- **Day 10**: ABC < 0.015, TAC < 0.015
- **Day 5**: ABC < 0.015, TAC < 0.015
- **Day 4**: ABC < 0.015, TAC < 0.015
- **Day 3**: ABC < 0.015, TAC < 0.015
- **Day 2**: ABC < 0.015, TAC < 0.015
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- **Day 11**: ABC 0.48, TAC 0.427

**RESULTS**

- **ART levels were consistent with adherence to antiretrovirals including a switch in**
  - for P1 (changed from ABC/3TC/DTG to TAF/FTC + DTG at Day 24) (Table 1)
  - Participants were compliant with DSF that was easily detectable in participant pills.
  - Initial examination of plasma samples revealed detectable levels of DSF that were low. Reasons for this are being investigated further.
  - VOR was detected at 24 and 48 hours post administration.

**Participants**

- **Participant 1**: 76 yo male, ART: Abacavir / Lamivudine / Dolutegravir
  - CD4 762 cells/µL, HIV RNA < 50 cp/mL for 4 yrs
  - Neuroimaging: sagittal sinus thrombosis and vertebral artery occlusion
  - Treatment: study meds ceased, anticoagulated, symptoms resolved by day 29

- **Participant 2**: 67 yo male, ART: Abacavir / Lamivudine / Dolutegravir
  - Treatment: study meds ceased, symptoms resolved by day 23

**Clinical course**

- **Day 19**: Admitted with memory impairment, emotional lability, lethargy and ataxia.
  - Day 24 admitted with confusion, lethargy, and ataxia.
  - Neuroimaging: sagittal sinus thrombosis and vertebral artery occlusion.
  - Day 23: With anticoagulation.

**Imaging**

- **Day 29**: Day 24 admitted with confusion, lethargy, and ataxia.

**PK / PD Assessments**

- Plasma concentrations of ART, VOR, DSF levels were also assessed in the tablets taken by the participants.

**METHODS**

**Figure 1. Clinical Trial Design:** Prospective single arm study of 28 days of disulfiram 2 g/day with intermittent vorinostat in HIV-infected individuals on suppressive ART

**Statistical Analysis**

- Primary endpoint: increase in plasma HIV RNA on day 11 relative to baseline.
- Sample size: Based on a mean HIV RNA of 1 cpg/ml and a standard deviation of 11 copies/mL in HIV-infected individuals on ART prior to any intervention, an increase in plasma HIV RNA of 10 copies/mL with 80% power at a 0.05 significance level would require 14 participants.

**Virological Assessments**

- Cell associated (CA) unspliced (US) and multiply spliced (MS) RNA and HIV DNA in CD4+ T-cells from blood
- HIV RNA in plasma using a single copy assay
- p24 expression in CD4+ T-cells by SIma
- Histone acetylation (HA) by flow cytometry from PBMCs

**REFERENCES**

3) Mota TM et al. No adverse safety or virological changes two years following vorinostat in HIV-infected individuals on antiretroviral therapy. AIDS 2017. 31(8):1137-1141.