Short-term Disulfiram to Reverse Latent HIV Infection: a Dose Escalation Study

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Background
Disulfiram has been used for the treatment of alcohol dependence for more than 80 years. It is an anticonvulsant, used daily and well tolerated in the absence of alcohol.

The current licensed dose is 500mg daily, but up to 1g per day has been given to overcome large inter-individual variations in drug exposure.

Disulfiram was identified in a high-throughput screen of compounds that inhibit HIV viral gene expression without cellular activation using a de-2-transduced primary CD4+ T cell model [2,3]. The precise mechanism of action is not known, but may be mediated via transduced primary CD4+ T cell model [1,2].

Induce HIV viral gene expression without cellular activation using a Bcl-2–Disulfiram was identified in a high-throughput screen of compounds that inhibit HIV viral gene expression without cellular activation using a de-2-transduced primary CD4+ T cell model [2,3].

The objective of this phase I/IIa pilot study was to determine the safety and tolerability of short-term disulfiram administration at a range of doses, and to assess the impact of disulfiram on latent HIV RNA in humanized mouse models and primary human T cells.

Methods
Short-term disulfiram administration in humans was safe and well-tolerated, even at doses four times the currently approved dose.

Disulfiram resulted in prolonged increases in CA-US HIV RNA at all doses and in plasma HIV RNA at high dose.

Prolonged increases in CA-US HIV RNA and plasma HIV RNA in subgroups with high baseline CA-US HIV RNA and high exposure to disulfiram or metabolites

Prior to any intervention, CA-US HIV RNA, but not HIV DNA or plasma HIV RNA (data not shown), was significantly higher immediately prior to the first dose of disulfiram. The reason for this is unclear but we propose an effect of circadian rhythms or stress on HIV transcription.

In a post hoc analysis, participants with high baseline CA-US HIV RNA and high exposure to disulfiram or its metabolites had significant and prolonged increases in CA-US HIV RNA and plasma HIV RNA.

As was observed in our pilot study [6], there was an apparent post-dosing effect. Cell-associated HIV RNA levels were consistently lower in the 1 day to 3 days after the last dose. Similar post-dosing effects have been observed with vorinostat and panobinostat.

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Given an excellent safety profile, disulfiram may be suited for future studies of combination therapy to activate latent HIV.

Conclusions
Disulfiram at high doses induced a prolonged increase in plasma HIV RNA consistent with promoting latency.