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

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on behalf of the Disulfiram Study investigators

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Abstract 428LB

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## Background

Disulfiram has been used for the treatment of alcohol dependence for more than sixty years. It is an oral agent, dosed daily and well tolerated in the absence of alcohol.

The current licensed dose is 500mg daily, but up to 6g 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 induce HIV viral gene expression without cellular activation using a Bcl-2–transduced primary CD4+ T cell model [1,2].

The precise mechanism of action is not known, but may be mediated via AKT and PTEN [2,3].

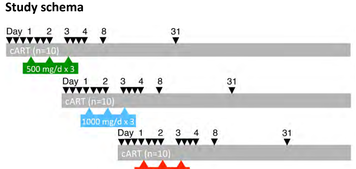
In an earlier pilot clinical study 14 days of disulfiram was given at the standard dose of 500mg daily to 16 adults on suppressive ART [4]. In that study, there was no *overall* significant change in plasma viremia, but plasma viremia was significantly higher a) in the *post-dosing period* compared to pre-dosing levels, and b) in the *sub-group* of participants with disulfiram detected at any time point (post-hoc analysis).

We conducted a dose escalation study to safely optimize drug exposure and better establish the effect of disulfiram on latent HIV infection.

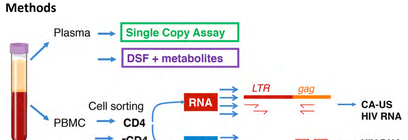
## Study design

- **Key eligibility**
  - HIV RNA<50 ≥ 3 yrs
  - CD4>350 cells/µl
  - No alcohol on study
- **Primary endpoints**
  - Safety and tolerability
  - Cell-associated unspliced (CA-US) HIV RNA in CD4 T-cells
- **Secondary endpoints**
  - Plasma HIV RNA (SCA)
  - HIV DNA
  - PK/PD

**Study schema**




**Methods**

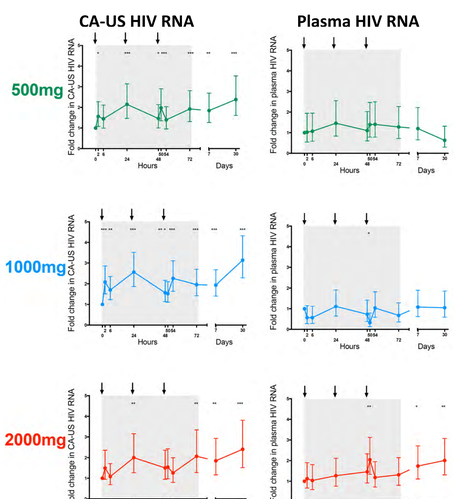



## Disulfiram was well tolerated at all doses

| Cohort | 500mg (n=10) | | 1000mg (n=10) | | 2000mg (n=10) | |
|---|---|---|---|---|---|---|
| Grade | 1 | 2 | 1 | 2 | 1 | 2 |
| **Headache** | | | 2 | | 3 | |
| **Drowsiness/lethargy** | | | 2 | | 2 | |
| **Light headedness** | | | | | 3 | |
| **Dry mouth/dysgeusia** | | | 3 | | 4 | |
| **Abdominal pain** | | | | | | |
| **Nausea** | | | 3 | | 2 | |
| **Diarrhoea** | | | | | | |
| **Hypophosphataemia** | 3 | | 2 | | | 2 |

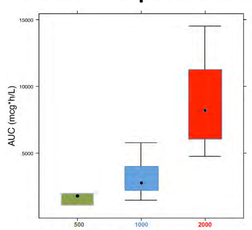
Adverse events possibly, probably or definitely related to study drug.
Hypophosphataemia events due to measurements within reference range of local laboratory, but qualifying as Grade 2 events as per DAIDS Adverse Event Table.
Baseline characteristics: mean age 52.8 years, 28/30 male and median baseline CD4 count 630 cells/µl.

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



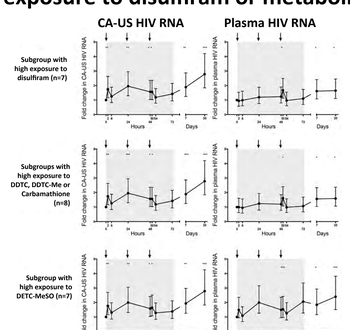

Each time point is compared to the mean of three pre-disulfiram time points. Bold arrows indicate the three disulfiram doses. ***p<0.001; **p<0.01 – 0.001; *p<0.05 – 0.01.

## Disulfiram administered at 2000 mg demonstrated supra-proportional increase in exposure to disulfiram



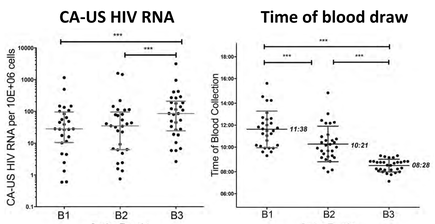

Pharmacokinetic modeling of relationship between disulfiram dose and cumulative area under the curve exposure to disulfiram. Disulfiram given at 2000 mg demonstrated a 48% higher-than-dose-proportional increase in drug exposure.

## 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



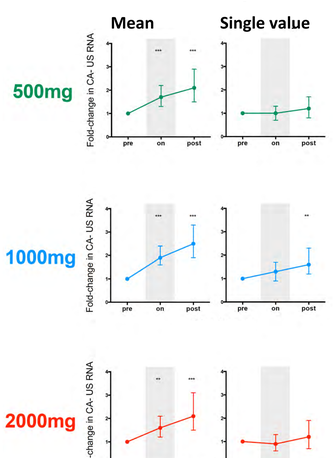

Subgroups with above median baseline CA-US HIV RNA and above median exposure (AUC) to disulfiram or metabolites: disulfiram → DDTC [N,N-diethyldithiocarbamate] → DDTC-Me [diethyldithiocarbamate-methyl ester] → DETC-MeSO [S-methyl-N,N-diethylthiolcarbamate sulfoxide] → Carbamathione. ***p<0.001; **p<0.01 – 0.001; *p<0.05 – 0.01.

## Baseline variability in CA-US HIV RNA




B1: screening visit; B3: blood draw immediately prior to first dose; B2: study visit between B1 and B3. ***p<0.001

## Estimate of effect of disulfiram on CA-US HIV RNA is influenced by choice of baseline




Mean: average of the three pre-dose time points; Single time point: blood draw immediately prior to first dose (B3) ***p<0.001; **p<0.01 – 0.001; *p<0.05 – 0.01.

## Summary

Short-term administration of disulfiram 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.

Disulfiram administered at 2000 mg demonstrated supra-proportional increases in disulfiram exposure compared to increases observed from 500 mg to 1000 mg.

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 [4], there was an apparent post-dosing effect. Cell-associated HIV RNA levels were consistently highest on Day 31, 28 days after the last dose. Similar post-dosing effects have been observed with vorinostat and panobinostat.

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.

## Conclusions

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

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

**Disulfiram Study Investigators**
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