Reviewer’s report

Title: Anti-HIV-1 activity of cellulose acetate phthalate: Synergy with soluble CD4 and induction of "dead-end" gp41 six-helix bundles

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Reviewer: Dr Carol Weiss

Level of interest: A paper whose findings are important to those with closely related research interests

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Neurath et al. report on new aspects of the mechanism by which cellulose acetate phthalate (CAP) inhibits HIV-1 infectivity. The authors previously reported that CAP does not interfere with gp120 binding to CD4 but instead blocks the co-receptor binding site on gp120. In the present study they address the question of whether CAP can still block gp120 interactions with coreceptor once gp120 is already bound to CD4 and whether CAP induced conformational changes in gp41. In ELISA experiments, the authors provide data showing that treatment with sCD4 increases CAP binding to gp120 and HIV-1 virions and that CAP appears to induce formation of the gp41 six-helix bundle in the absence of CD4. They also present data indicating that sCD4 and CAP inhibit infection synergistically.

The authors present a series of rational experiments with conclusions that are supported by the data. The methods are straightforward and adequate detail is provided, but inclusion of additional controls in some experiments would make the arguments stronger. The authors should comment on the following:
- Interpretation of results in Fig. 1 would be clearer if it was determined whether sCD4 binds CAP and if a dose-response curve to increasing concentrations of sCD4 with a fixed about of gp120 was provided.
- Experiments in Fig. 5 would be more complete if a negative control peptide were included and specificity for the CCR5R binding site could determined if the CCR5 S-peptide were tested on the X4 virus.
- Additional control antibodies in Fig. 6, such as HIV+ sera or gp41 antibodies specific for native or receptor-activated envelope glycoprotein, would help confirm the affects of CAP binding on envelope glycoprotein structure. Quantifying the amount of gp120 shed after CAP treatment would also provide independent support for induction of conformational changes by CAP.
- In virion binding experiments, the authors should discuss how sCD4-induced shedding of gp120 from virions might affect the results. Conceivably, the increased CAP binding of BaL virions versus IIIB virions in Fig. 2 reflects more CD4-induced gp120 shedding of the IIIB envelope compared to BaL.
- Fig. 8 and its discussion are not well integrated with the main points of the paper.

The most significant finding--that CAP, in the absence of CD4, induces conformational changes leading
to formation of the six-helix bundle--has important implications for the development of novel antivirals against HIV. It suggests that agents that bind near the chemokine receptor binding site of gp120 can cause irreversible inhibition of HIV, even in the absence of CD4. The implications of the second main point, that CAP can bind to gp120 after sCD4 treatment, is less clear because virion binding to soluble receptor in an ELISA assay may not adequately take into account the high avidity interactions between Env oligomers and receptors on target cells or kinetic issues relating to virus entry vs. CAP binding that take place during infection. Nonetheless, the finding that sCD4 and CAP can bind gp120 simultaneously and synergistically inhibit virus infection reveal an advance in our understanding the mechanism of CAP inhibition.

**Competing interests:**

None declared.