

# Review of: "[Perspective] Hypochlorous Acid (HOCl): A Multifaceted and Promising Therapeutic Perspective Against Human Immunodeficiency Virus (HIV)"

Doris Loh

Potential competing interests: No potential competing interests to declare.

This perspective investigates the potential of using hypochlorous acid (HOCl) as a therapeutic adjunct during early-phase HIV infection. The review discusses molecular mechanisms of HOCl that may be able to target pathogenic mechanisms employed by the HIV virus. The authors suggest a short-term feasibility study to evaluate the clinical application of calcium hypochlorite as a source of HOCl in HIV disease treatment.

The perspective, although innovative in concept, lacks substantial work that is required to demonstrate potential efficacy of HOCl in HIV-1 treatment. The authors may wish to consider including the following topics for discussion that can potentially improve content and validity:

1. Effectiveness - Early in vitro experiments on HIV-1 and sodium hypochlorite found that adequate concentrations of chlorine were necessary to effectively inactivate the virus. "In the presence of 80% blood, 1000 p.p.m. available chlorine in the disinfectant test mixture was unable to inactivate 3.75 log TCID<sub>50</sub> HIV/ml, although 2500 p.p.m. available chlorine was able to inactivate at least 1.5 log TCID<sub>50</sub> HIV/ml. In all test mixtures, the chlorine rapidly became combined and thus less active." [Van Bueren J, Simpson RA, Salman H, Farrelly HD, Cookson BD. Inactivation of HIV-1 by chemical disinfectants: sodium hypochlorite. *Epidemiol Infect.* 1995 Dec;115(3):567-79. doi: 10.1017/s0950268800058738. PMID: 8557089; PMCID: PMC2271608.] Hence, when considering clinical application for HOCl, it may be necessary to define a minimum effective dosage range for calcium hypochlorite.
2. HIV-1 viral life cycle - The conclusion states that "HOCl offers a unique mechanism of action, targeting the virus and associated pathogens at multiple stages of their life cycles." However, the viral life cycle of HIV-1 was never discussed in the article. It is important for readers to understand there may be limitations to the effectiveness of HOCl application. The molecular mechanisms described in this article appear only to affect the initial binding and fusion stages during the HIV-1 viral life cycle. Moreover, the timing of this window may be quite restrictive. "We find that HIV requires an average of 52 h between export of virions in one generation to export in the next, with most of this (33 h) taken up by reverse transcription." [Murray JM, Kelleher AD, Cooper DA. Timing of the components of the HIV life cycle in productively infected CD4<sup>+</sup> T cells in a population of HIV-infected individuals. *J Virol.* 2011 Oct;85(20):10798-805. doi: 10.1128/JVI.05095-11. Epub 2011 Aug 10. PMID: 21835801; PMCID: PMC3187481.]

Therefore, it may be helpful to discuss how the molecular mechanism of HOCl may or may not affect the HIV-1 virus at respective stages of its life cycle.

3. Rapid turnover - The HIV-1 virus is known for the extremely rapid turnover of plasma virions.[Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995;373(6510):123-126. doi:10.1038/373123a0] “The mean estimated half-life of plasma virions was 5 min, significantly shorter than previous estimates.”[Murray et al. 2011] Thus, the window of opportunity for HOCl may be prohibitively short in duration.
4. Latency - The ability of the HIV-1 virus to remain dormant and undetected inside infected immune cells is perhaps one of the most challenging issues in the management of HIV-1 infections. A brief discussion on this topic may be beneficial for readers to understand the potential limitations of HOCl therapy.
5. Safety of HOCl - The paper mentions the selective reactivity of HOCl towards molecular targets within microbial cells, with the implication that HOCl “does not pose a significant risk to human cells at therapeutic concentrations.” The endogenous production of HOCl, catalyzed by the enzyme myeloperoxidase, has been linked with an extensive list of pathologies. [Andrés CMC, Pérez de la Lastra JM, Juan CA, Plou FJ, Pérez-Lebeña E. Hypochlorous Acid Chemistry in Mammalian Cells-Influence on Infection and Role in Various Pathologies. *Int J Mol Sci*. 2022;23(18).] It may be beneficial for readers to include a discussion on how the use of calcium hypochlorite may affect individuals with pre-existing health conditions that can potentially be exacerbated by HOCl application.