Roda, Weston C.; Liu, Suli; Power, Christopher; Li, Michael Y.

Summary: Combination antiretroviral therapy (cART) has greatly increased life expectancy for human immunodeficiency virus-1 (HIV-1)-infected patients. Even given the remarkable success of cART, the virus persists in many different cells and tissues. The presence of viral reservoirs represents a major obstacle to HIV-1 eradication. These viral reservoirs contain latently infected long-lived cells. The “shock and kill” therapeutic strategy aims to reactivate latently infected cells by latency reversing agents (LRAs) and kill these reactivated cells by strategies involving the host immune system. The brain is a natural anatomical reservoir for HIV-1 infection. Brain macrophages, including microglia and perivascular macrophages, display productive HIV-1 infection. A mathematical model was used to analyze the dynamics of latently and productively infected brain macrophages during viral infection and this mathematical model enabled prediction of the effects of LRAs applied to the “shock and kill” strategy in the brain. The model was calibrated using reported data from simian immunodeficiency virus (SIV) studies. Our model produces the overarching observation that effective cART can suppress productively infected brain macrophages but leaves a residual latent viral reservoir in brain macrophages. In addition, our model demonstrates that there exists a parameter regime wherein the “shock and kill” strategy can be safe and effective for SIV infection in the brain. The results indicate that the “shock and kill” strategy can restrict brain viral RNA burden associated with severe neuroinflammation and can lead to the eradication of the latent reservoir of brain macrophages.

MSC: 92C50 Medical applications (general)

Keywords: HIV-1; SIV; viral dynamics; brain macrophage; combination antiretroviral therapy (cART); shock and kill strategy; multiple equilibria

Software: Matlab

Full Text: DOI

References:
[3] Asahchop, EL; Meziane, O.; Mamik, MK; Chan, WF; Branton, WG; Resch, L.; Gill, MJ; Hodsdod, E.; Guimond, JV; Wainberg, MA; Baker, GB; Cohen, EA; Power, C., Reduced antiretroviral drug efficacy and concentration in hiv-infected microglia contributes to viral persistence in brain. Retrovirology (2017) doi:10.1186/s12977-017-0370-5
[5] Avalos, CR; Price, SL; Forsyth, ER; Pin, JN; Shirk, EN; Bullock, BT; Queen, SE; Li, M.; Gellerup, D.; O’Connor, SL; Zink, MC; Mankowski, JL; Gama, L.; Clements, JE, Quantitation of productively infected monocytes and macrophages of simian immunodeficiency virus-infected macaques, J Virol, 90, 12, 5643-5656 (2016) doi:10.1128/JVI.00290-16
[6] Azevedo, FAC; Carvalho, LRB; Grinberg, LT; Farfel, JM; Ferretti, REL; Leite, REP, Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain, J Comp Neurol, 513, 532-541 (2009) doi:10.1002/cne.21974


[40] Luget, V.; Narasipura, SD; Barbian, HI; Richards, M.; Wallace, J.; Razmpour, R.; Buzhdygan, T.; Ramirez, SH; Prevedel, L.; Eugenin, EA; AI-Harthi, L., Hiv infects astrocytes in vivo and egresses from the brain to the periphery, PLoS Pathog, 16, 6, e1008381 (2020) - doi:10.1371/journal.ppat.1008381

[41] Meulendyke, KA; Queen, SE; Engle, EL; Shirk, EN; Liu, J.; Steiner, JP; Nath, A.; Tarwater, PM; Graham, DR; Mankowski, JL; Zink, MC, Combination fluconazole/paroxetine treatment is neuroprotective despite ongoing neuroinflammation and viral replication in an siv model of hiv neurological disease, J Neurovirol, 20, 6, 591-602 (2014) - doi:10.1080/02648725.2013.840283


[44] Roda, WC; Li, MY; Akimunwi, MS; Assuchop, EL; Gelman, BB; Witwer, KW; Power, C., Modeling brain lentiviral infections during antiretroviral therapy in aids, J Neurovirol, 23, 4, 577-586 (2017) - doi:10.1007/s13468-017-0530-3


[47] Singer, EJ; Nemann, NM; Shapshak, P.; Levine, A.; Buzhdygan, T.; Ramirez, SH; Prevedel, L.; Eugenin, EA; Al-Harthi, L., Hiv infects astrocytes in vivo and egresses from the brain to the periphery, PLoS Pathog, 16, 6, e1008381 (2020) - doi:10.1371/journal.ppat.1008381


This reference list is based on information provided by the publisher or from digital mathematics libraries. Its items are heuristically matched to zbMATH identifiers and may contain data conversion errors. It attempts to reflect the references listed in the original paper as accurately as possible without claiming the completeness or perfect precision of the matching.